WHO Technical Report Series

1035

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2021 (including the 22nd WHO Model List of Essential Medicines and the 8th WHO Model List of Essential Medicines for Children)

World Health Organization

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Executive summary

The meeting of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines took place virtually and was hosted in Geneva, Switzerland, from 21 June to 2 July 2021. The aim of the meeting was to review and update the 21st WHO Model List of Essential Medicines (EML) and the 7th WHO Model List of Essential Medicines for Children (EMLc), the Model Lists.

The Expert Committee considered a total of 88 applications, including 40 proposals for the addition of 38 new medicines or medicine classes, 16 proposals for new indications for 32 currently listed medicines, 13 proposals for the addition of new formulations of 19 currently listed medicines, and three proposals for the removal of 19 medicines or formulations on the Model Lists. In accordance with applicable procedures[1], the Expert Committee evaluated the scientific evidence for the comparative effectiveness, safety and cost–effectiveness of the medicines in question. The Committee also considered a review of the therapeutic alternatives for medicines on the Model Lists (square box listings), an update to the AWaRe (Access–Watch–Reserve) classification of antibiotics to support stewardship activities, a review of the available evidence for CAR-T cell therapies for B-cell lymphoma, and reports on insulin pricing and access, and switching between originator and similar biotherapeutic products (biosimilars).

The Expert Committee did not consider any applications for the inclusion of medicines for the treatment or prevention of coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has seen the quick evolution of knowledge on a previously unknown disease, rapidly evolving clinical hypotheses and proposals of potential treatments. As knowledge accumulates within an emergency framework for a pathogen that is rapidly evolving, the quality of the evidence necessarily also changes over short time frames. This scenario does not fit within the intended aim of the EML, which has a longer-term scope and gives much weight to the certainty of the value of selected medicines. In the emergency context, WHO recommendations on best-available treatments are presented as part of WHO guidelines. However, this scenario might evolve and therapeutic options for COVID-19 may be considered for inclusion in Model Lists in the future.

In summary, the Expert Committee:

- recommended the addition of 20 new medicines to the EML (13 to the core list and seven to the complementary list);
- recommended the addition of 17 new medicines to the EMLc (12 to the core list and five to the complementary list);
- recommended adding additional indications for 28 currently listed medicines;
- recommended the addition of new formulations of 23 currently listed medicines;
- recommended the deletion of two medicines and of specific formulations of a further 13 medicines;

[1] http://www.who.int/selection_medicines/committees/subcommittee/2/eeb1098%5b1%5d.pdf

- updated 72 square box listings, removed the square box from seven listings, and recommended a review of a further 23 square box listings; and
- did not recommend 25 proposals for inclusion, change or deletion for 28 medicines, medicine classes or formulations.

The recommended changes bring the total number of medicines (including fixed-dose combinations) on the EML to 479 (from 460 in 2019), including 350 on the EMLc (from 336 in 2019). The total number of listed medicines takes into account the additions and deletions, as well as changes made as a result of the revision of therapeutic equivalent alternatives.

The recommendations are briefly described below in order of their appearance on the Model Lists.

A full summary of changes to the Model Lists is shown in Table 1. Applications not recommended are shown in Table 2.

Section 4: Antidotes and other substances used in poisonings

Section 4.2 Specific

The Expert Committee did not recommend listing for N-acetylcysteine for the new indication of non-paracetamol-induced acute liver failure based on very low certainty of the available evidence and heterogeneity in the results, making confidence in the estimates of benefit in this indication limited.

Section 5: Anticonvulsants/antiepileptics

The Expert Committee recommended the inclusion of a cautionary note with the listings for valproic acid (sodium valproate) on the EML and EMLc, to avoid use in pregnancy and in females of child-bearing potential, unless alternative treatments are ineffective or not tolerated, due to the high risk of birth defects and developmental disorders in children exposed to valproate in the womb. The Committee did not recommend transferring the listings of valproic acid from the core to the complementary list due to concerns that doing so may reduce access and undermine the important role of this medicine in the management of epilepsy and bipolar disorder. This recommendation also applies to the listing on the EML for valproic acid in Section 24.2.2 Medicines used in bipolar disorders.

Section 6: Anti-infective medicines

Section 6.1.4 (NEW) Cysticidal medicines

The Expert Committee recommended inclusion of albendazole, mebendazole and praziquantel on the complementary list of the EML and EMLc for the new indication of treatment of diseases caused by taeniid cestode infections. Albendazole and mebendazole are recommended for treatment of cystic echinococcosis and alveolar echinococcosis; albendazole and praziquantel are recommended for treatment of neurocysticercosis. The Committee noted that these medicines are considered treatments of choice for these neglected tropical diseases and are recommended in current WHO guidelines.

Section 6.2.1 Access group antibiotics
Section 6.2.2 Watch group antibiotics
Section 6.2.3 Reserve group antibiotics

The Expert Committee recommended the inclusion of cefiderocol on the EML for treatment of adults with multidrug resistant infections due to carbapenem-resistant Enterobacterales and carbapenem-resistant *Pseudomonas aeruginosa* and endorsed cefiderocol as a Reserve antibiotic in the AWaRe classification. The Committee noted that cefiderocol is one of the few medicines that has activity against carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, which are ranked as "Critical Priority" on the WHO Priority Pathogens List. Cefiderocol was shown to be non-inferior to carbapenems with regard to microbiological/clinical response and mortality (with the possible exception of infections due to carbapenem-resistant *Acinetobacter* spp., where higher mortality has been observed in patients receiving cefiderocol) in settings where there are few alternatives for multidrug-resistant Gram-negative organisms producing metallo-betalactamases. The Committee highlighted the importance of antibiotic stewardship activities to assure appropriate use, while preserving access for patients in need of this medicine.

The Committee did not recommend empiric use of any antibiotics for the treatment of bronchitis and bronchiolitis, noting that these infections are usually caused by respiratory viruses and the available evidence does not suggest benefit of antibiotic use compared with placebo and symptomatic treatment.

The Committee: recommended empiric antibiotic treatment options for endophthalmitis (ceftazidime, ceftriaxone and vancomycin), necrotizing fasciitis (ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin), neonatal meningitis (gentamicin) and intra-abdominal infections in children (ampicillin and gentamicin); revised the existing treatment recommendations for lower urinary tract infections (removing amoxicillin as a recommended treatment) and skin and soft tissue infections (recommending cefalexin as a first-choice treatment option); and recommended the addition of new strength formulations for a number of currently listed antibiotics. The Committee also endorsed the current listings on the EML and EMLc for systemic and topical antibiotic treatment of trachoma, and topical antibiotic treatment of bacterial blepharitis, conjunctivitis and keratitis.

Section 6.2.5 Antituberculosis medicines

The Expert Committee recommended the inclusion of new strength, child-friendly formulations of bedaquiline and delamanid on the EMLc for the treatment of multidrug-resistant tuberculosis in children.

The Committee recommended inclusion of a new strength formulation of rifapentine and a fixed-dose combination formulation of rifapentine + isoniazid on the EML and EMLc for tuberculosis preventive treatment (previously known as treatment for latent tuberculosis infection) to reduce the pill burden and improve treatment adherence to WHO-recommended tuberculosis preventive treatment regimens.

The Committee recommended inclusion of rifapentine and moxifloxacin on the core list of the EML for the new indication of treatment of drug-susceptible tuberculosis, in line with updated WHO recommendations for a 4-month treatment regimen comprising rifapentine, isoniazid, pyrazinamide and moxifloxacin as an alternative to the standard 6-month regimen with rifampicin, isoniazid, pyrazinamide and ethambutol. The Committee also recommended inclusion of a new strength formulation of pyrazinamide on the EML and EMLc for use in treatment regimens for drug-susceptible tuberculosis, which will offer a reduced pill burden for patients.

The Committee did not recommend the addition of injectable formulations of ethambutol, isoniazid and rifampicin to the EML and EMLc for the treatment of tuberculosis in specific patient populations, notably patients with severe forms of tuberculosis associated with poor outcomes, patients with acute or chronic gastrointestinal disease or malabsorption disorders, patients with severe comorbidities, and patients unable or unwilling to take oral dosage forms. The Committee judged as insufficient the evidence presented in the applications on differences in terms of important benefits (e.g. mortality) between oral and injectable formulations by severity of illness. Important factors influencing this decision included the consistent preference for oral treatment for tuberculosis instead of intravenous administration in WHO guideline recommendations, the limited availability of these formulations in most countries, the potential for unnecessary use of intravenous formulations, and related hospitalization in patients otherwise able to take oral therapy.

The Committee recommended deletion from the EML and EMLc of various formulations and strengths of amikacin, amoxicillin + clavulanic acid, isoniazid, isoniazid + pyrazinamide + rifampicin, linezolid, p-aminosalicylic acid and pyrazinamide, noting that they are not optimal formulations and strengths for tuberculosis treatment, in line with recommendations in current WHO treatment guidelines. The Committee recommended the addition of new injection solution formulations for amikacin, which have the advantage over powder for injection formulations of not requiring reconstitution for administration. The Committee did not recommend deletion of the oral liquid formulations of ethambutol, isoniazid and pyrazinamide, nor a 125 mg tablet formulation of ethionamide at this time, due to concerns about limited uptake and availability of preferred dispersible tablet formulations in some countries.

Section 6.3 Antifungal medicines

The Expert Committee recommended the inclusion of the echinocandin antifungal micafungin (with a square box indicating caspofungin and anidulafungin as therapeutic alternatives) on the complementary list of the EML and EMLc for the empiric treatment of suspected or proven invasive *Candida* infections in adults and children. The evidence presented suggested that echinocandins were associated with greater treatment success when compared with amphotericin B or triazole antifungals and supported the use of echinocandins in the empiric treatment of suspected or proven invasive *Candida* infections in critically ill patients, especially where there is a high probability of azole resistance. Furthermore, echinocandin antifungals were associated with a more favourable tolerability profile compared with non-echinocandin antifungals (e.g. amphotericin B). The Committee did not support listing for indications of

prophylaxis of invasive *Candida* infections, nor treatment of invasive *Aspergillus* infections due to more limited evidence and the availability of effective alternatives already included on the Model Lists.

Section 6.4.2 Antiretrovirals

The Expert Committee recommended the inclusion of a new strength, child-friendly formulation of dolutegravir on the EMLc for the treatment of HIV infection in children. The Committee also recommended the deletion of various formulations and strengths of abacavir, atazanavir, efavirenz, lamivudine, lamivudine + nevirapine + zidovudine, lopinavir + ritonavir, raltegravir, and ritonavir from the EML and/or EMLc, in line with recommendations in WHO HIV treatment guidelines and the updated Optimal Formulary and Limited-Use list for Antiretroviral Drugs for Children. The Committee did not recommend listing the fixed-dose combination formulation of abacavir + lamivudine + lopinavir/ritonavir, noting that this formulation did not demonstrate bioequivalence with the reference product and does not yet have regulatory approval.

Section 6.4.3 Other antivirals

The Committee recommended deletion of oseltamivir oral powder formulation from the complementary list of the EML and EMLc, noting that this formulation is no longer manufactured or marketed.

Section 6.4.4.2 Medicines for hepatitis C

The Expert Committee recommended the inclusion of fixed-dose combinations of daclatasvir + sofosbuvir, glecaprevir + pibrentasvir and sofosbuvir + velpatasvir, as well as single agent daclatasvir and single agent sofosbuvir to the core list of the EMLc for the treatment of children with chronic hepatitis C virus infection, based on evidence of pan-genotypic effectiveness and acceptable safety. The Committee also recommended the inclusion of the fixed-dose combination of daclatasvir + sofosbuvir on the core list of the EML.

Section 7: Antimigraine medicines

Section 7.1 For treatment of acute attack

The Expert Committee recommended inclusion of sumatriptan on the core list of the EML for the treatment of adult patients with acute migraine. Sumatriptan is associated with improvements in clinically meaningful outcomes such as pain freedom, headache relief and reduction in the use of rescue medication. Compared with acetylsalicylic acid and paracetamol, the analgesics currently included in the Model Lists for acute migraine treatment, sumatriptan has a different toxicity profile, and may offer long-term safety advantages, particularly in patients who experience frequent migraine attacks. The Committee considered that, overall, the available evidence indicated a positive benefit to risk profile for sumatriptan and that listing would provide an additional treatment option for patients who cannot tolerate or do not respond adequately to alternative analgesics already listed.

Section 8: Immunomodulators and antineoplastics

Section 8.1 Immunomodulators for non-malignant disease

The Expert Committee recommended the inclusion of tacrolimus on the complementary list of the EML and EMLc for use as maintenance immunosuppression following organ transplantation, based on evidence of a favourable benefit to harm ratio. Tacrolimus significantly reduces acute rejection and graft loss when compared with ciclosporin, an alternative listed in the EML, and it has a different toxicity profile. The Committee recognized the public health importance of survival of transplanted organs and transplant recipients, given the shortage of donor organs and the significant investment of resources associated with organ transplantation.

Section 8.2 Antineoplastic and supportive medicines

A total of 23 applications for cancer medicines were received from various sources. Several applications were the product of efforts of the EML Cancer Medicines Working Group to engage with expert stakeholders to identify and prioritize the most effective cancer medicines for indications where they have clinically relevant benefits, in line with the criteria established by the Expert Committee in 2019 for magnitude of clinical benefit (European Society of Medical Oncology – Magnitude of Clinical Benefit Scale (ESMO-MCBS) score) and median overall survival gain (at least 4 to 6 months median).

Applications for both the inclusion of new cancer medicines as well as for new indications for currently listed cancer medicines were considered by the Expert Committee. All applications were also reviewed by the EML Cancer Medicines Working Group prior to the meeting, which provided written comments to inform the Expert Committee's considerations. The Committee also considered a review of the available evidence for CAR-T cell therapy for relapsed/refractory diffuse large B-cell lymphoma, in which no request was made for inclusion on the Model Lists at this time.

The Expert Committee recommended listing for the following new medicines and/or new indications.

Recommendations for inclusion of new cancer medicines

– Inclusion of enzalutamide on the complementary list of the EML as a therapeutic alternative to abiraterone for treatment of metastatic castration-resistant prostate cancer. Enzalutamide appears to demonstrate comparable efficacy to abiraterone, has a different mechanism of action and a different toxicity profile, and may be an option for patients unable to be treated with abiraterone. Enzalutamide and abiraterone are both oral treatments but enzalutamide is administered as monotherapy, while abiraterone is co-administered with corticosteroids to reduce toxicity and requires regular monitoring of liver enzymes. The availability of different treatment options with similar efficacy may provide opportunities for countries to negotiate better prices as part of their national procurement processes.

- Inclusion of everolimus on the complementary list of the EML and EMLc for the treatment of subependymal giant cell astrocytoma associated with tuberous sclerosis complex in patients, mostly children, who are not eligible for surgery. The recommendation was based on limited evidence indicating a favourable benefit to harm ratio in a patient population for whom an unmet clinical need exists. Everolimus is associated with relevant reductions in tumour volume and improved control of resulting disorders (seizures, developmental delays). The Expert Committee did not endorse the use of everolimus for indications other than subependymal giant cell astrocytoma.
- Inclusion of ibrutinib on the complementary list of the EML for the treatment of relapsed/refractory chronic lymphocytic leukaemia (with and without chromosome 17p deletion), based on evidence of a major sustained benefit in terms of overall survival and progression-free survival, less acute toxicity, and minimal risk of secondary leukaemias compared with chemoimmunotherapy. The Committee noted that targeted therapy with ibrutinib is replacing chemoimmunotherapy as the accepted standard of care in the treatment of chronic lymphocytic leukaemia. The Committee acknowledged the potential role for ibrutinib in the first-line treatment setting, but considered that the available evidence, while promising, was currently immature and therefore did not recommend listing for first-line treatment at this time. The Committee would welcome a submission with updated survival data in the first-line treatment setting for consideration at its next meeting.
- Inclusion of rasburicase on the complementary list of the EML and EMLc for the prevention and treatment of tumour lysis syndrome. The Committee noted that rasburicase can markedly and rapidly decrease uric acid levels, and is associated with relevant clinical advantages over allopurinol (currently listed for this indication) in terms of efficacy outcomes and safety in paediatric and adult patients at high risk of tumour lysis syndrome. The Committee noted the high cost of rasburicase, and acknowledged numerous experimental studies suggesting that a single-dose treatment regimen is likely to be as effective as daily treatment for 5 days in lowering uric acid levels, at a much lower cost.

Recommendations for new indications for existing listed cancer medicines

- Current listings of carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine on the complementary list of the EML and EMLc be extended to include the new indication of low-grade glioma. These medicines are recognized as the standard of care for low-grade glioma. Their benefits and harms are well known from extensive use in adults and in other indications for children.
- The current listing for carboplatin on the complementary list of the EML be extended to include the new indication of head and neck cancer as a radio-sensitizer. Listing of carboplatin for this indication provides an alternative option for patients unable to tolerate cisplatin.

- The current listing for imatinib on the complementary list of the EML and EMLc be extended to include the new indication of Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia, based on evidence of a relevant survival benefit compared with conventional chemotherapy and acceptable safety.
- The current listing for vinorelbine on the complementary list of the EML be extended, and vinorelbine be included on the complementary list of the EMLc for treatment of rhabdomyosarcoma in children and adolescents at high risk of relapse. Maintenance treatment with vinorelbine in combination with cyclophosphamide demonstrated relevant survival benefits and acceptable toxicity. The Committee also recommended the addition of new oral formulations of vinorelbine to the EML and EMLc.
- Additional indications were recommended for 12 cancer medicines currently included on the EMLc for treatment of various cancers in children. Efficacy and safety were accepted based on extrapolation of the well-known benefits and harms of use of these medicines in adults, for other indications in children, and as part of standard cancer care in children. Refer to Table 1 for details.

The Expert Committee did not recommended listing for the following new medicines and/or new indications:

- Azacitidine for the treatment of acute myeloid leukaemia in adults, due to lack of a clinically relevant survival benefit compared with listed medicines, such as cytarabine and daunorubicin, and substantial toxicity.
- BRAF and MEK inhibitor combinations (dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib) for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. The Committee noted that BRAF/MEK inhibitor combinations are associated with important gains in terms of overall survival, but the magnitude of benefit is not as large as that seen with immunotherapies such as nivolumab and pembrolizumab, which are currently listed and remain the preferred therapy for metastatic melanoma. The Committee also noted that the limited availability of genomic testing to identify patients with tumours carrying the BRAF V600 mutation could be a potential barrier to access and appropriate use in many settings.
- Cyclin-dependent kinase 4/6 inhibitors abemaciclib, palbociclib and ribociclib for the treatment of hormone receptor positive/human epidermal growth factor receptor (HER2)-negative advanced or metastatic breast cancer, in combination with endocrine therapy (aromatase inhibitors, tamoxifen or fulvestrant). The Committee noted that based on the available evidence, these medicines appear to be associated with a positive benefit to harm ratio, but that survival data, while promising, are currently immature. Particularly in the first-line setting, it is not yet confirmed if improvements in disease-free survival will translate to an overall survival benefit in the long term. There is also uncertainty about optimal

dose and duration of therapy and use in early-stage disease, and whether relevant clinical differences exist between agents within the pharmacological class. Additionally, the Committee noted that at the current high prices, these medicines have not been found to be cost-effective and would pose serious affordability challenges, especially in low-resource settings. The Committee would welcome a resubmission, with updated survival data at its next meeting.

– Daratumumab for the treatment of newly diagnosed and relapsed/refractory multiple myeloma. The Committee acknowledged that daratumumab was associated with a consistent and clinically important survival benefit, in first-line, newly diagnosed, transplant eligible and transplant ineligible, and relapsed/refractory multiple myeloma. Adding daratumumab to conventional therapy was associated with a modest increase in toxicity. However, the Committee noted that the available evidence was not yet mature, with trial follow-up still ongoing. The Committee would welcome a resubmission, with updated survival data at its next meeting. The Committee also noted that at current prices, daratumumab is prohibitively expensive and has not been found to be cost-effective, even in high-income settings. The Committee was also concerned about the potential budget impact of listing daratumumab, which would be used as part of regimens that include other expensive medicines, i.e. bortezomib and lenalidomide, included on the EML since 2019.
– Doxorubicin for the treatment of rhabdomyosarcoma, based on evidence of an unfavourable benefit to harm ratio.
– Fulvestrant for the treatment of hormone receptor positive/HER2-negative metastatic breast cancer because of low-certainty evidence of survival benefit, compared with aromatase inhibitors and the need for longer follow-up data. Furthermore, multiple medicines (e.g. aromatase inhibitors, tamoxifen) are currently included on the EML for treatment of endocrine-responsive breast cancer. In addition, the Committee noted the high price of fulvestrant and the likely very large eligible patient population, which would have a significant financial impact on both patients and health systems.
– Osimertinib for first-line treatment of epidermal growth factor receptor (EGFR)-mutated locally advanced or metastatic non-small-cell lung cancer. Despite evidence that indicates the third-generation tyrosine kinase inhibitor osimertinib to have meaningful overall survival benefit compared with the first- and second-generation tyrosine kinase inhibitors currently listed on the EML (erlotinib, gefitinib and afatinib), the available data are currently immature, limiting confidence in the actual magnitude of benefit. In addition, at the current high price, osimertinib has not been found to be cost-effective and would pose serious affordability challenges, especially in low-resource settings. The Committee considered whether osimertinib could be included as a therapeutic alternative under the current listing for erlotinib but decided against this option due to the risk of considerable additional expenditure at the country level when the currently listed tyrosine kinase inhibitors are likely to be more affordable

and accessible, with some generics currently available. The Committee would welcome a resubmission, with updated survival data at its next meeting.

– PD-1/PD-L1 immune checkpoint inhibitors (atezolizumab, durvalumab, nivolumab, pembrolizumab) for the treatment of non-oncogene addicted, locally advanced or metastatic non-small-cell lung cancer. The Committee acknowledged that these medicines are associated with a relevant median overall survival benefit as first-line treatment, well over the EML threshold of 4 to 6 months, based on evidence from several studies, and have substantially improved outcomes for the treatment of non-small-cell lung cancer in practice. The greatest benefits are reported in the population of patients whose tumours have high (≥ 50%) PD-L1 expression. The addition of PD-1/PD-L1 immune checkpoint inhibitors to conventional chemotherapy was associated with modest increases in toxicity, which may require highly specialized management in selected cases. Overall, the Committee considered that these medicines had a favourable benefit to harm ratio. However, listing was not recommended because at current prices, these medicines are prohibitively expensive in many settings. The issue of treatment costs and appropriate use of these medicines is further complicated by the need for diagnostic testing to identify patients most likely to benefit, uncertainties about the optimal duration of treatment, the significant disease burden and the likely large eligible patient population. The Committee considered that the financial implications of listing PD 1/PD-L1 immune checkpoint inhibitors for this indication would result in unstainable expenditures for many patients and health systems.
– Pertuzumab for use in combination with trastuzumab and taxane chemotherapy for first-line treatment of HER2-positive unresectable or metastatic breast cancer. The Committee accepted that pertuzumab, in combination with trastuzumab and a taxane, is associated with relevant overall survival benefits. However, the Committee noted that survival benefit is limited to the metastatic setting, with uncertainty about the clinical benefit in early-stage breast cancer. Pertuzumab and trastuzumab are both highly priced medicines and, despite trastuzumab having been included on the EML since 2015 and the availability of WHO prequalified biosimilars, access and affordability of trastuzumab remains very limited in resource-constrained settings. The Committee was concerned that also adding pertuzumab to the EML would result in considerable additional expenditure at the country level, diverting resources that should be prioritized for improving access to and affordability of trastuzumab, which is highly effective across all breast cancer stages.
– Tislelizumab, an anti-PD-1 monoclonal antibody, for the treatment of Hodgkin lymphoma, due to the availability of only limited efficacy and safety data from early phase trials, no comparative evidence of efficacy and safety versus other treatments, the current high price and unknown cost–effectiveness. The Committee would welcome a resubmission when mature survival data for tislelizumab, and data on the comparative efficacy of tislelizumab and other

immune checkpoint inhibitors in the treatment of Hodgkin lymphoma are available.

- Tislelizumab for the treatment of urothelial carcinoma in patients with high PD-L1 expression who have failed prior platinum-based chemotherapy, due to the availability of only limited efficacy and safety data from early phase trials, no comparative evidence of efficacy and safety versus other treatments, the current high price and unknown cost–effectiveness.
- Zanubrutinib, a Bruton tyrosine kinase inhibitor, for the treatment of relapsed/refractory chronic lymphocytic leukaemia, due to the availability of only limited efficacy data from early phase trials, with small patient numbers and short follow-up, significant toxicity concerns, and unlikely cost–effectiveness at the reported price. The Committee would welcome a resubmission, with more mature survival data and evidence of comparative effectiveness and safety in relation to other EML listed medicines for chronic lymphocytic leukaemia, at its next meeting.
- Zanubrutinib for the treatment of relapsed/refractory mantle cell lymphoma, due to the availability of only limited efficacy data from early phase trials, significant toxicity concerns, no comparative evidence of efficacy and safety versus other treatments, and unlikely cost–effectiveness at the reported price.

Review of evidence for CAR-T therapy for diffuse large B-cell lymphoma

The Expert Committee considered a review of the available evidence for chimeric antigen receptor (CAR)-T cell therapy for treatment of relapsed or refractory diffuse large B-cell lymphoma. Notably, this review did not propose inclusion of CAR-T cell therapies on the Model Lists at this time, and the Committee was not required to make any recommendation for listing. The Committee noted that CAR-T cell therapy is very highly specialized, requiring dedicated health system resources well beyond those currently available in most settings. Current treatment and management costs are also prohibitively high, exceeding affordability thresholds in almost all countries.

The Committee acknowledged that currently, the available evidence is limited and of very low certainty. Nevertheless, it was noted that the immature data from multiple studies indicate that CAR-T cell therapy can induce durable complete responses which may lead to clinical cures in some patients. Currently, the main uncertainties about the clinical benefits of CAR-T therapy relate to the proportion of patients achieving long long-term disease-free survival, and when CAR-T cell therapy is best deployed in the overall treatment algorithm. Safety concerns include cytokine release syndrome and neurological toxicity, both of which occur in a high proportion of patients, may be life-threatening and require highly specialized medical management. Data on long-term safety are currently limited.

The Committee considered that CAR-T cell therapies are an area of significant interest and therapeutic relevance in the treatment of diffuse large B-cell lymphoma, and potentially other indications. The Committee considered that the evidence base for these therapies should continue to be monitored by WHO on an ongoing basis. If future evidence is favourable, there

will be need for a strong leadership and advocacy role for WHO in facilitating affordable and equitable access to these treatments.

Section 13: Dermatological medicines

Section 13.4 Medicines affecting skin differentiation and proliferation

The Expert Committee recommended the inclusion of topical calcipotriol on the core list of the EML and EMLc for the treatment of moderate forms of psoriasis. Listing was recommended with calcitriol and tacalcitol as therapeutic alternatives. The Committee noted evidence that calcipotriol is effective compared to placebo, but not superior to topical corticosteroids. It has a favourable safety profile compared with topical corticosteroids due to low systemic absorption. Calcipotriol may be a beneficial alternative treatment in patients who are unable to use or tolerate topical corticosteroids.

Section 15: (RENAMED) Antiseptics and disinfectants

The Expert Committee did not recommend inclusion of hypochlorous acid solution on the EML and EMLc for use in antisepsis and wound decontamination. The clinical effectiveness evidence was sparse, and results were judged to be inconclusive, primarily due to heterogeneity in study design and small study sizes. The Committee would welcome a future resubmission including data from ongoing studies and a more structured and systematic review of the literature.

With regard to use of hypochlorous acid solution as an environmental disinfectant, the Committee noted that the Model Lists currently includes hypochlorous acid as part of the broader class – chlorine-based compounds. The Committee recommended that this listing should be amended to specify the different recommended formulations to provide greater clarity for national selection. With this recommended amendment, the Committee considered that a separate listing for the proposed formulation of hypochlorous acid solution was not necessary.

Section 18: Medicines for endocrine disorders

The Expert Committee did not recommend inclusion of simvastatin on the EML for the new indication of treatment of polycystic ovary syndrome. The Committee considered that while the available evidence suggests simvastatin is associated with improvements in biochemical markers in patients with polycystic ovary syndrome, there was inadequate evidence of improvement in relevant clinical outcomes. The Committee also noted that simvastatin use is contraindicated in pregnancy due to risk of harm to the fetus. As polycystic ovary syndrome mainly affects women of reproductive age and one aim of treatment of polycystic ovary syndrome is to improve fertility, the Committee considered that this was an important safety concern.

Section 18.5.1 Insulins

The Committee recommended inclusion of long-acting insulin analogues (insulin detemir, insulin degludec and insulin glargine, and their quality-assured biosimilars, as therapeutic alternatives) on the core list of the EML and EMLc for the treatment of patients with type 1 or type 2 diabetes mellitus who are at high risk of experiencing hypoglycaemia with human insulin.

The current application was the fourth time that the Expert Committee has considered long-acting insulin analogues for inclusion on the EML and EMLc. The Committee again acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet, achieving reliable, equitable and affordable access to insulin remains a significant public health challenge in many countries. Once again, the available evidence showed that the magnitude of clinical benefit of long-acting insulin analogues over human insulin for most clinical outcomes was small, making the large price differential between insulin analogues and human insulin difficult to justify. However, the Committee considered that the observed benefits of insulin analogues over human insulin with regard to lower incidence of symptomatic and nocturnal hypoglycaemia were consistent and clinically important, particularly for the subset of patients at high risk of hypoglycaemia, justifying the decision to recommend inclusion.

The Committee noted that insulin prices offered to patients and procurers differ considerably among countries. Long-acting insulin analogues are often much more expensive than human insulin. However, overall use of analogues seems to be expanding and prices are decreasing for those no longer under patent protection. Some countries are implementing dedicated policy actions on insulin prices to increase affordability and access. In settings where cost-containment actions and efficient negotiations are in place, prices for insulin analogues are decreasing and aligning with those of human insulin.

The Committee noted and shared the concerns expressed by several stakeholders related to potential effects of the inclusion of insulin analogues on the Model Lists on the human insulin market, currently dominated by three pharmaceutical companies, and the financial implications for patients and health systems where insulin analogues are not available or affordable. The Committee was unequivocal that affordable access to human insulin remains a critical priority globally.

The Committee noted that significant efforts made by WHO to seek expressions of interest for prequalification of human insulin had not resulted in the submission of dossiers from any manufacturers. However, an interest by manufacturers in a prequalification process that includes more types of insulin has emerged. The inclusion of insulin analogues on the Model Lists represents a first step that can facilitate the insulin prequalification process, if insulin analogues are included in the call for expressions of interest. The Committee considered that this could lead to prequalified human and analogue insulins becoming available, and an increase in the number of insulin manufacturers. The Committee encourages WHO to evaluate the impact of the EML listing of insulin analogues on global availability, accessibility and price of insulins. The Committee also highlighted the importance of commitment and action from Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally.

Section 18.5.2 Oral hypoglycaemic agents

The Expert Committee recommended inclusion of the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin (with canagliflozin and dapagliflozin as therapeutic alternatives) on the core list of the EML as add-on treatment for adults with type 2 diabetes with or at high risk of cardiovascular disease and/or diabetic nephropathy. This recommendation was based on high-

quality evidence of reduced risk of all-cause mortality, major cardiovascular adverse events and adverse renal outcomes, and a reasonable safety profile.

Section 19: Immunologicals

Section 19.2 (RENAMED) Sera, immunoglobulins and monoclonal antibodies

The Expert Committee recommended inclusion of equine rabies immunoglobulin and anti-rabies virus monoclonal antibodies to the core list of the EML and EMLc for use as part of rabies postexposure prophylaxis, in line with WHO recommendations and on the basis of a favourable benefit to harm ratio. The Committee considered that the availability of a range of alternative options on the Model Lists for use in rabies postexposure prophylaxis would facilitate access to treatment, which remains suboptimal in many settings. In addition, the inclusion of anti-rabies monoclonal antibodies will potentially address some of the supply and production limitations currently experienced with both human and equine rabies immunoglobulin.

Section 19.3 Vaccines

This section was reviewed by the Secretariat for consistency and full alignment with the latest WHO recommendations for routine immunization (September 2020). No changes to the current vaccine listings on the EML and EMLc were required.

Section 22: Medicines for reproductive health and perinatal care

Section 22.1.6 Intravaginal contraceptives

The Expert Committee recommended inclusion of ethinylestradiol + etonogestrel contraceptive vaginal ring to the core list of the EML, based on evidence of comparable contraceptive efficacy and tolerability compared with combined oral contraceptives. The Committee noted that the combined contraceptive vaginal ring is included as a contraceptive option in the WHO guidance on medical eligibility criteria for contraceptive use, and considered that inclusion on the EML supports the principle of choice for patients in the provision of family planning and contraception.

Section 22.5 Other medicines administered to the mother

The Expert Committee recommended inclusion of multiple micronutrient supplement tablets on the core list of the EML for use as an antenatal supplement in pregnant women, based on public health need and evidence of benefit in pregnancy outcomes including reduced risk of stillbirth, low and very low birth weight, small for gestational age births, and preterm births compared with iron and folic acid supplementation. The Committee considered the financial impact on health systems associated with multiple micronutrient supplements was likely to be small. The Committee acknowledged the WHO guideline recommendations for use of multiple micronutrient antenatal supplements only in a research-specific context. The Committee considered that inclusion on the EML may facilitate and should not prevent such research.

Section 24: Medicines for mental and behavioural disorders

The Expert Committee welcomed and supported the proposal from the WHO Department of Mental Health and Substance Use for a comprehensive revision of the mental health chapter on the EML and EMLc to be carried out in the next biennium to ensure that the Model Lists are updated and consistent with existing WHO recommendations for the management of mental health disorders.

The Expert Committee did not recommend inclusion of methylphenidate on the EML and EMLc for the treatment of attention deficit hyperactivity disorder (ADHD). The current application was the second time that the Expert Committee considered methylphenidate, following a recommendation not to include it in 2019 due to uncertainties in the estimates of benefit and concerns about the quality and limitations of the available evidence for benefit and harm.

New evidence was presented from a network meta-analysis of trials evaluating the comparative efficacy and tolerability of medicines for ADHD. However, the Committee considered that the updated evidence, in continuity with relevant limitations of previous data, still did not support inclusion of methylphenidate on the Model Lists. The Committee considered that methylphenidate is associated with relatively large reductions in symptom with short-term use. However, the benefit to harm ratio of methylphenidate remained uncertain for long-term use while the medication carries significant risks. Specifically, the Committee noted that most of the included studies in the network meta-analysis in both children/adolescents and adults were judged to have an unclear or high risk of bias. In addition, there were few included studies that measured outcomes beyond 12 weeks of treatment, which the Committee considered was a major limitation, given that ADHD is a longer-term condition and treatment is usually administered for months to years. In addition, the Committee considered that the outcome measure of tolerability, defined as the proportion of patients who dropped out of studies because of adverse effects, did not provide adequate information on the frequency and severity of specific adverse effects associated with methylphenidate use. The Committee advised that evidence of the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration, outcomes of the revision of the WHO mhGAP guidelines, and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings would be informative for any future consideration for inclusion of methylphenidate on the Model Lists.

Section 24.1 Medicines used in psychotic disorders

The Expert Committee recommended the inclusion of paliperidone 1-month long-acting injection, with a square box indicating risperidone long-acting injection as a therapeutic alternative, to the core list of the EML for maintenance treatment of schizophrenia in adults stabilized on oral therapy. The Committee noted that the effectiveness and overall safety of first- and second-generation antipsychotics is similar. The Committee considered that the availability of different treatment alternatives was important to meet the public health need for such treatments, particularly given the uncertainty of the current and future availability of fluphenazine injection, currently the only long-acting antipsychotic injection included on the

EML. The Committee also noted the public health need for long-acting antipsychotics in settings where close follow-up of patients with psychotic disorders is difficult.

Section 24.5: Medicines for disorders due to psychoactive substance use

The Expert Committee recommended the inclusion of bupropion and varenicline on the core list of the EML for use as an aid to smoking cessation, based on evidence of acceptable benefit to risk ratios, in an area of major public health need. Currently, the only smoking cessation therapy included on the EML is nicotine replacement therapy. The Committee noted that varenicline has been shown to be more effective than bupropion, but the Committee considered that the availability of different smoking cessation treatments with different toxicity profiles would provide valuable options and choice for both patients and clinicians. In addition, the Committee considered that the inclusion of different pharmacological interventions on the EML for smoking cessation could facilitate increased market competition, reduce costs and improve access for national health systems. The Committee also noted that the success of pharmacological interventions for quitting smoking is optimized when patients are prepared to quit and receive quit advice, education, counselling and support from health care providers. Therefore, a comprehensive approach to smoking cessation should be optimized at the country level, together with strengthening of national tobacco control policies.

Section 29: Medicines for diseases of joints

Section 29.2 (RENAMED) Disease-modifying anti-rheumatic drugs (DMARDs)

The Expert Committee recommended inclusion of hydroxychloroquine on the complementary list of the EML for the treatment cutaneous lupus erythematosus, based on evidence of a favourable overall benefit to harm ratio compared with other available treatments (e.g. corticosteroids). The Committee noted that the main safety concern related to long-term use of hydroxychloroquine is increased risk of irreversible retinopathy and therefore recommended that availability of ophthalmological monitoring be a condition for its use.

The Committee noted that hydroxychloroquine is currently only included on the EMLc for the treatment of systemic lupus erythematosus in children. The Committee accepted that hydroxychloroquine is also an established and effective disease-modifying treatment option for systemic lupus erythematosus in adults and recommended that hydroxychloroquine should also be included on the complementary list of the EML for this indication.

Section 29.3 Juvenile joint diseases

The Expert Committee considered three applications for the inclusion of new medicines for the treatment of juvenile joint diseases and recognized the public health relevance of effective treatments for these diseases.

The Committee did not recommend inclusion of anakinra for the treatment of children with systemic onset juvenile idiopathic arthritis (SOJIA) with macrophage activation syndrome (MAS), nor tocilizumab for the treatment of children with SOJIA because of uncertainty in the estimates

of clinical benefits, as well as concerns about access and affordability in different settings, noting these are both highly priced medicines. The Committee acknowledged that other treatments of SOJIA are recommended in guidelines and used in clinical practice (e.g. methotrexate, adalimumab, canakinumab) but these were not considered in the application, limiting the Committee's ability to identify treatments with the best risk–benefit profile.

The Committee did not recommend inclusion of triamcinolone hexacetonide for the treatment of juvenile idiopathic arthritis, due to concerns about the quality of evidence, risks associated with the intra-articular injection procedure and limited generalizability of findings from high-income settings to low- and middle-income settings. The Committee considered that evidence on the role and comparative benefits and risks of intra-articular corticosteroids compared with oral corticosteroids or disease-modifying anti-rheumatic drugs would be informative in any future consideration.

The Committee noted the proposal received from the Paediatric Global Musculoskeletal Task Force for changes to the presentation of previous recommendations for medicines for joint diseases in children on the EMLc and the electronic EML. In response, the Committee recommended that Section 29.2 "Disease-modifying agents used in rheumatoid disorders (DMARDs)" be renamed "Disease modifying anti-rheumatic drugs (DMARDs)". However, the Committee recommended that any further changes should be deferred at this time and requested that a comprehensive review of this section of the Model Lists be undertaken for the next Expert Committee meeting.

Section 30: (NEW) Dental preparations

The Expert Committee recommended the establishment of a new section on the EML and EMLc for dental preparations. The Committee noted that the burden of oral diseases, particularly untreated dental caries, represents a significant public health problem globally.

In consideration of the application requesting inclusion of fluoride toothpaste on the core list of the EML and EMLc, the Committee recommended that the current listing for sodium fluoride be transferred from Section 27 (Vitamins and Minerals) to the new section for dental preparations. The listing should be amended to 'fluoride', noting that topical fluoride-containing preparations utilize fluoride in a variety of forms. Fluoride toothpaste is recommended for inclusion as a specifically defined formulation of fluoride (paste, cream or gel containing between 1000 and 1500 ppm fluoride, any type) because of its proven effectiveness in preventing dental caries and for better control of the quality of fluoride content. The Committee requested WHO to identify and define the alternative fluoride-containing formulations that are recommended for use in the prevention of dental caries so that these can be specifically indicated in the Model Lists in 2023 to provide clear guidance to countries.

The Committee also recommended inclusion of glass ionomer cement and silver diamine fluoride preparations on the core list of the EML and EMLc for the prevention and treatment of dental caries. The Committee noted that these products offer relevant benefits and can be used in atraumatic restorative treatment techniques and in non-specialized settings in alignment with WHO guidance on oral health interventions.

Other matters considered by the Expert Committee

Highly priced medicines

Throughout the meeting, the Expert Committee noted the trend of continually increasing prices of new medicines over time, particularly in the areas of cancer, autoimmune diseases, infectious diseases and rare diseases. Among new highly priced medicines, few offer additional relevant benefits sufficient to reach the status of essential medicines.

However, some of these medicines are associated with large, clinically relevant benefits and favourable safety profiles, yet the prohibitively high price – multiples of median annual household incomes making them unaffordable even in high-income countries – has delayed or prevented the Committee from recommending inclusion on the Model Lists. The problem of affordability is not only limited to new medicines, as some "old" highly effective medicines, such as insulins, are also often priced at a level that represents a major barrier to access given the need for chronic, sometimes lifelong, treatment.

The Committee highlighted the ongoing challenge of making such medicines more affordable for the people and communities who need to access them. For low- and middle-income countries, this is especially important given that the number of people living with diseases that may require these medicines is steadily increasing.

The Committee recommended establishing a standing EML Working Group to support the Expert Committee to provide advice to WHO on policies and rules to make highly priced essential medicines more affordable and accessible. Tasks of the Working Group should include:

- exploration of thresholds at which specific essential medicines become affordable in relation to countries' and patients' ability to pay;
- identification of prices that represent "fair value" for the benefits expected from essential medicines;
- identification of interventions by policy-makers and other actors that could facilitate relevant and rapid decreases in prices to reach universal access to these treatments; and
- development of a strategy to monitor price and availability trends of essential but unaffordable medicines, to be proposed as part of the next WHO General Programme of Work.

The Working Group should collaborate closely with groups within WHO and other external stakeholders working to increase affordability and transparency of prices and costs of health products.

The Committee reiterated the important role of the Medicines Patent Pool in facilitating affordable access to essential medicines through negotiation of public health-oriented licences with patent holders to allow generic manufacture and supply of medicines in low- and middle-income countries. The Committee welcomed the expansion of the Medicines Patent Pool's mandate to patented essential medicines beyond HIV, hepatitis C and tuberculosis, to include

other small molecules included in the Model Lists, and medicines with strong potential for future inclusion. Among the new medicines recommended for inclusion on the Model Lists at this meeting, the Committee requested the Medicines Patent Pool explore licensing possibilities for enzalutamide, ibrutinib and the SGLT2 inhibitors. A number of patented medicines were not recommended for inclusion on the Model Lists at this meeting, either because they were considered not to be cost-effective at current prices, or because the available evidence was promising but not yet sufficiently mature. However, the Committee considered that cyclin-dependent kinase 4/6 inhibitors, daratumumab, osimertinib, PD 1/PD-L1 immune checkpoint inhibitors and zanubrutinib all had potential for future inclusion and recommended the Medicines Patent Pool explore the application of its licensing model to these medicines.

Switching between originator and similar biological products

The Expert Committee considered reports of the available evidence for switching between originator and similar biological products (biosimilars) of antitumour necrosis factor (TNF) biologicals, erythropoietins and insulins. The Committee noted that a substantial body of evidence exists that the switch from originators to biosimilars for anti-TNF medicines does not affect safety, immunogenicity and efficacy in a variety of conditions. More limited evidence suggests similar conclusions for erythropoietins and insulin analogues. Differences in discontinuation rates in open-label studies comparing originators with biosimilars are often driven by the so-called nocebo effect due to patients' negative expectations with regard to biosimilars and not the pharmacological action of the medicine itself.

The Committee considered that reducing uncertainties about the use of biosimilars and supporting strategies promoting interchangeability at the procurement and clinical level have a great potential to increase global access to effective biological medicines. For the biological medicines included on the Model Lists, the Committee recommended that quality-assured biosimilars should be considered interchangeable and eligible for selection and procurement at the country level for national essential medicines lists (see also Review of square box listings, below).

Review of square box listings

The square box symbol is intended to indicate similar clinical performance of different medicines within a pharmacological class, and that suitable therapeutic alternatives may be considered for selection at the country level for national essential medicines lists. The Committee recognized that considerable heterogeneity exists in the Model Lists with the use and application of both the square box symbol and other ad hoc notes intended to indicate acceptable therapeutic alternatives.

To provide greater clarity for national EML selection committees, the Committee recommended that the square box listing concept should be used consistently and exclusively, replacing notes where they exist. In addition, square box listings should be qualified to explicitly indicate the recommended therapeutic alternatives. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or therapeutic subgroup, defined at the fourth level

of the Anatomical Therapeutic Chemical (ATC) classification. The Committee therefore endorsed proposals made by the Secretariat for amendments and reviews of current square box listings. Refer to Table 1 for details.

For biological medicines, the Committee considered that quality-assured biosimilars represent appropriate therapeutic alternatives to originator biologicals for selection at the country level. In the same way that the square box is not used to indicate alternative generic brands of the same small molecule medicines, the square box should not be used to indicate alternative quality-assured biosimilars of biological medicines. Nevertheless, the Committee recognized that increased availability of biosimilars could lead to greater market competition, improved access and reduced costs for patients and health systems. To support the uptake of quality-assured biosimilars, the Committee recommended that listings for biological medicines on the Model Lists should include a separate note specifying that quality-assured similar biological products are appropriate alternatives to consider for selection at the country level.

Finally, the Committee recommended that the square box symbol should be removed from the Model Lists in 2023 and replaced with specific references to the accepted therapeutic alternatives.

Update to the AWaRe classification of antibiotics

The Expert Committee noted the increasing uptake and utilization of the AWaRe classification of antibiotics by Member States, and the efforts being made to achieve the country-level target of 60% of total antibiotic consumption being Access group antibiotics.

The Committee acknowledged the contributions of the EML Antibiotics Working Group to review and update the AWaRe classification with newly registered antibiotics and antibiotics not previously classified. The Committee endorsed the Working Group's recommendations for the update of the AWaRe classification. An additional 81 antibiotics were classified (40 as Access, 34 as Watch and seven as Reserve) and will be included in the 2021 update of the AWaRe classification database.

The Committee also noted the request from the WHO Department of Global Coordination and Partnership (Division of Antimicrobial Resistance) for a comprehensive review of Reserve group antibiotics currently included on the Model Lists, as well as newly approved Reserve group antibiotics. The Committee agreed that providing more focused guidance for WHO Member States on which antibiotics should be considered essential from a public health perspective and included in national access programmes would be beneficial. The Committee therefore requested the Secretariat and the EML Antibiotics Working Group to undertake this review for consideration by the Committee at the next meeting.

All applications and documents reviewed by the Expert Committee are available on the WHO website at: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee

Table 1
Recommended additions, changes and deletions on the 2021 EML and EMLc

EML – New medicines added		EMLc – New medicines added	
Medicine	**Indication**	**Medicine**	**Indication**
Anti-rabies virus monoclonal antibodies	Rabies postexposure prophylaxis	Anti-rabies virus monoclonal antibodies	Rabies postexposure prophylaxis
Bupropion	Smoking cessation	☐ Calcipotriol	Psoriasis
☐ Calcipotriol	Psoriasis	Daclatasvir	Hepatitis C
Cefiderocol	Infection due to multidrug-resistant pathogens	Daclatasvir + sofosbuvir	Hepatitis C
☐ Empagliflozin	Type 2 diabetes mellitus	Equine rabies immunoglobulin	Rabies postexposure prophylaxis
Equine rabies immunoglobulin	Rabies postexposure prophylaxis	Everolimus	Subependymal giant cell astrocytoma
Everolimus	Subependymal giant cell astrocytoma	Glass ionomer cement	Dental caries
Glass ionomer cement	Dental caries	Glecaprevir + pibrentasvir	Hepatitis C
Hydroxychloro-quine	Cutaneous lupus erythematosus, systemic lupus erythematosus	☐ Long-acting insulin analogues	Type 1 and 2 diabetes in patients at high risk of hypoglycaemia
Ibrutinib	Relapsed/refractory chronic lymphocytic leukaemia	☐ Micafungin	Invasive *Candida* infection
☐ Long-acting insulin analogues	Type 1 and 2 diabetes in patients at high risk of hypoglycaemia	Rasburicase	Tumour lysis syndrome
☐ Micafungin	Invasive *Candida* infection	Silver diamine fluoride	Dental caries
Multiple micronutrient supplement	Antenatal supplement	Sofosbuvir	Hepatitis C
☐ Paliperidone	Schizophrenia	Sofosbuvir + velpatasvir	Hepatitis C

Table 1 *continued*

EML – New medicines added		**EMLc – New medicines added**	
Medicine	**Indication**	**Medicine**	**Indication**
Rasburicase	Tumour lysis syndrome	Tacrolimus	Organ transplant rejection
Silver diamine fluoride	Dental caries	Trimethoprim	Lower urinary tract infection
Sumatriptan	Migraine	Vinorelbine	Rhabdomyosarcoma
Tacrolimus	Organ transplant rejection		
Trimethoprim	Lower urinary tract infection		
Varenicline	Smoking cessation		

EML – New/changed indications		**EMLc – New/changed indications**	
Albendazole	Diseases caused by taeniid cestode cysts	Albendazole	Diseases caused by taeniid cestode cysts
Carboplatin	Head and neck cancer (as a radio-sensitizer), low-grade glioma, nephroblastoma, ovarian germ cell tumours, testicular germ cell tumours	Ampicillin	Complicated intra-abdominal infections
Ceftazidime	Endophthalmitis	Carboplatin	Low-grade glioma, nephroblastoma, ovarian germ cell tumours, testicular germ cell tumours
Ceftriaxone	Endophthalmitis, necrotizing fasciitis	Ceftazidime	Endophthalmitis
Cisplatin	Low-grade glioma	Ceftriaxone	Endophthalmitis, necrotizing fasciitis
Clindamycin	Necrotizing fasciitis	Cisplatin	Low-grade glioma
Cyclophospha-mide	Low-grade glioma, nephroblastoma	Clindamycin	Necrotizing fasciitis
Dactinomycin	Ewing sarcoma	Cyclophospha-mide	Low-grade glioma, nephroblastoma

Table 1 *continued*

EML – New/changed indications		EMLc – New/changed indications	
Dexamethasone	Burkitt lymphoma	Dactinomycin	Ewing sarcoma
Etoposide	Acute myeloid leukaemia, nephroblastoma, osteosarcoma	Dexamethasone	Burkitt lymphoma
Hydrocortisone	Burkitt lymphoma	Etoposide	Acute myeloid leukaemia, nephroblastoma, osteosarcoma
Ifosfamide	Burkitt lymphoma, nephroblastoma	Gentamicin	Complicated intra-abdominal infections, neonatal meningitis
Imatinib	Ph+ acute lymphoblastic leukaemia	Hydrocortisone	Burkitt lymphoma
Irinotecan	Nephroblastoma, rhabdomyosarcoma	Ifosfamide	Burkitt lymphoma, nephroblastoma
Mebendazole	Diseases caused by taeniid cestode cysts	Imatinib	Ph+ acute lymphoblastic leukaemia
Mesna	Burkitt lymphoma, nephroblastoma	Irinotecan	Nephroblastoma, rhabdomyosarcoma
Methotrexate	Burkitt lymphoma	Mebendazole	Diseases caused by taeniid cestode cysts
Methylpredniso-lone	Burkitt lymphoma	Mesna	Burkitt lymphoma, nephroblastoma
Metronidazole	Necrotizing fasciitis	Methotrexate	Burkitt lymphoma
Moxifloxacin	Drug-susceptible tuberculosis	Methylpredniso-lone	Burkitt lymphoma
Ofloxacin	Conjunctivitis	Metronidazole	Necrotizing fasciitis
Piperacillin + tazobactam	Necrotizing fasciitis	Ofloxacin	Conjunctivitis
Praziquantel	Diseases caused by taeniid cestode cysts	Piperacillin + tazobactam	Necrotizing fasciitis
Rifapentine	Drug-susceptible tuberculosis	Praziquantel	Diseases caused by taeniid cestode cysts

Table 1 *continued*

EML – New/changed indications		EMLc – New/changed indications	
Vancomycin	Endophthalmitis, necrotizing fasciitis	Vancomycin	Endophthalmitis, necrotizing fasciitis
Vinblastine	Low-grade glioma	Vinblastine	Low-grade glioma
Vincristine	Low-grade glioma	Vincristine	Low-grade glioma
Vinorelbine	Rhabdomyosarcoma		

EML – New formulation/strength		EMLc – New formulation/strength	
Amikacin (Section 6.2.5 Antituberculosis medicines only)	Injection: 100 mg/2 mL, 250 mg/mL in 2 mL vial	Amikacin (Section 6.2.5 Antituberculosis medicines only)	Injection: 100 mg/2 mL, 250 mg/mL in 2 mL vial
Amoxicillin	Solid oral dosage form: 1 g	Bedaquiline	Tablet: 20 mg
Amoxicillin + clavulanic acid	Tablet: 875 mg + 125 mg	Cisplatin	Injection: 10 mg/10 mL, 20 mg/20 mL
Cefalexin	Solid oral dosage form: 500 mg	Cyclophospha-mide	Powder for injection: 1 g, 2 g in vial
Ceftriaxone	Powder for injection: 2 g	Delamanid	Tablet (dispersible): 25 mg
Ciprofloxacin	Solid oral dosage form: 500 mg	Dolutegravir	Tablet (dispersible, scored): 10 mg
Cisplatin	Injection: 10 mg/10 mL, 20 mg/20 mL	Isoniazid + rifapentine	Tablet (scored): 300 mg + 300 mg
Clindamycin	Injection: 600 mg/4 mL, 900 mg/6 mL	Pyrazinamide	Tablet: 500 mg
Cyclophospha-mide	Powder for injection: 1 g, 2 g in vial	Rifapentine	Tablet (scored): 300 mg
Daclatasvir + sofosbuvir	Tablet: 60 mg + 400 mg	Vinblastine	Injection: 10 mg (sulfate)/10 mL
Ethinylestradiol + etonogestrel	Vaginal ring: 2.27 mg + 11.7 mg	Vincristine	Injection: 1 mg (sulfate)/mL, 2 mg (sulfate)/2 mL
Isoniazid + rifapentine	Tablet (scored): 300 mg + 300 mg		
Phenoxymethyl-penicillin	Tablet: 500 mg		

Table 1 *continued*

EML – New formulation/strength		EMLc – New formulation/strength
Prednisolone	Retention enema: 200 mg/100 mL (as sodium phosphate)	
Pyrazinamide	Tablet: 500 mg	
Rifapentine	Tablet (scored): 300 mg	
Sofosbuvir	Tablet: 200 mg	
Vancomycin	Powder for injection: 500 mg, 1 g	
Vinblastine	Injection: 10 mg (sulfate)/10 mL	
Vincristine	Injection: 1 mg (sulfate)/mL, 2 mg (sulfate)/2 mL	
Vinorelbine	Capsule: 20 mg, 30 mg, 80 mg	

EML – Medicines/formulations deleted		EMLc – Medicines/formulations deleted	
Amikacin (Section 6.2.5 Antituberculosis medicines only)	Powder for injection: 100 mg, 500 mg, 1 g in vial	Abacavir	Tablet (dispersible): 60 mg
Atazanavir	Solid oral dosage form: 100 mg, 300 mg	Amikacin (Section 6.2.5 Antituberculosis medicines only)	Powder for injection: 100 mg, 500 mg, 1 g in vial
Efavirenz	Tablet (scored): 200 mg	Amoxicillin + clavulanic acid (Section 6.2.5 Antituberculosis medicines only)	Oral liquid: 125 mg + 31.25 mg/5 mL
Isoniazid	Tablet (scored): 50 mg	Atazanavir	Solid oral dosage form: 100 mg
Isoniazid + pyrazinamide + rifampicin	Tablet: 75 mg + 400 mg + 150 mg	Efavirenz	Tablet (scored): 200 mg

Table 1 *continued*

EML – Medicines/formulations deleted		EMLc – Medicines/formulations deleted	
Lamivudine + nevirapine + zidovudine	Tablet: 150 mg + 200 mg + 300 mg	Isoniazid	Tablet (scored): 50 mg
Linezolid (Section 6.2.5 Antituberculosis medicines only)	Injection for IV administration: 2 mg/mL in 300 mL bag Tablet: 400 mg	Lamivudine	Tablet: 150 mg
Lopinavir + ritonavir	Oral liquid: 400 mg + 100 mg/5 mL	Lamivudine + nevirapine + zidovudine	Tablet: 30 mg + 50 mg + 60 mg
Oseltamivir	Oral powder: 12 mg/mL	Linezolid (Section 6.2.5 Antituberculosis medicines only)	Injection for IV administration: 2 mg/mL in 300 mL bag Tablet: 400 mg
p-aminosalicylic acid	Tablet: 500 mg	Lopinavir + ritonavir	Oral liquid: 400 mg + 100 mg/5 mL
Pyrazinamide	Tablet (scored): 150 mg	Oseltamivir	Oral powder: 12 mg/mL
Raltegravir	Tablet (chewable): 100 mg	p-aminosalicylic acid	Tablet: 500 mg
Ritonavir	Oral liquid: 400 mg/5 mL	Pyrazinamide	Tablet (scored): 150 mg
		Raltegravir	Tablet (chewable): 100 mg Tablet: 400 mg
		Ritonavir	Oral liquid: 400 mg/5 mL Oral powder: 100 mg in sachet

Updated square box listings			
Section	**Medicine**	**Specified therapeutic alternatives**	**List**
1.1.2	Propofol	Thiopental	EML & EMLc
2.3	Ondansetron	Dolasetron, granisetron, palonosetron, tropisetron	EML & EMLc
3	Loratadine	Cetirizine, fexofenadine	EML & EMLc
3	Prednisolone	Prednisone	EML & EMLc
5	Lorazepam (parenteral)	Diazepam (parenteral), midazolam (parenteral)	EML & EMLc

Table 1 *continued*

Updated square box listings			
Section	**Medicine**	**Specified therapeutic alternatives**	**List**
6.2.1	Cloxacillin	Fourth level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)	EML & EMLc
6.2.2	Clarithromycin	Erythromycin as second choice treatment for pharyngitis	EMLc
6.2.2	Meropenem	Imipenem + cilastatin as second choice treatment for severe complicated intraabdominal infections and high-risk febrile neutropenia	EML & EMLc
6.2.5	Cycloserine	Terizidone	EML
6.2.5	Ethionamide	Protionamide	EML & EMLc
6.2.5	Meropenem	Imipenem + cilastatin	EML
6.4.1	Aciclovir	Valaciclovir	EML
6.4.2.5	Efavirenz + emtricitabine + tenofovir	Lamivudine (for emtricitabine component)	EML
6.4.2.5	Emtricitabine + tenofovir	Lamivudine (for emtricitabine component)	EML
6.5.1	Metronidazole	Tinidazole	EML & EMLc
8.2.4	Anastrozole	Fourth level ATC chemical subgroup (L02BG Aromatase inhibitors)	EML
8.2.4	Bicalutamide	Flutamide, nilutamide	EML
8.2.4	Leuprorelin	Goserelin, triptorelin	EML
8.2.4	Prednisolone	Prednisone	EML & EMLc
9	Biperiden	Trihexyphenidyl	EML
9	Levodopa + carbidopa	Benserazide (for carbidopa component)	EML
10.3	Deferoxamine	Deferasirox	EML & EMLc
12.1	Isosorbide dinitrate	Remove square box	EML
12.3	Amlodipine	Fourth level ATC chemical subgroup (C08CA Dihydropyridine derivatives)	EML
12.3	Enalapril	Fourth level ATC chemical subgroup (C09AA ACE inhibitors, plain)	EML & EMLc

Table 1 *continued*

Updated square box listings			
Section	**Medicine**	**Specified therapeutic alternatives**	**List**
12.3	Hydrochlorothiazide	Chlorothiazide, chlorthalidone, indapamide	EML
12.3	Lisinopril + amlodipine	Fourth level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril component) Fourth level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine component)	EML
12.3	Lisinopril + hydrochlorothiazide	Fourth level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril component) Indapamide, chlorthalidone, chlorothiazide (for hydrochlorothiazide component)	EML
12.3	Losartan	Fourth level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	EML
12.3	Telmisartan + amlodipine	Fourth level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan component) Fourth level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine component)	EML
12.3	Telmisartan + hydrochlorothiazide	Fourth level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan component) Indapamide, chlorthalidone, chlorothiazide (for hydrochlorothiazide component)	EML
12.4	Enalapril	Fourth level ATC chemical subgroup (C09AA ACE inhibitors, plain)	EML
12.4	Furosemide	Bumetanide, torasemide	EML
12.4	Hydrochlorothiazide	Chlorothiazide, chlorthalidone, indapamide	EML
12.4	Losartan	Fourth level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	EML

Table 1 *continued*

Updated square box listings			
Section	**Medicine**	**Specified therapeutic alternatives**	**List**
12.6	Simvastatin	Atorvastatin, fluvastatin, lovastatin, pravastatin	EML
13.1	Miconazole	Fourth level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	EML & EMLc
13.3	Betamethasone	Fourth level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	EML & EMLc
13.3	Calamine	Remove square box	EML
13.3	Hydrocortisone	Fourth level ATC chemical subgroup (D07AA Corticosteroids, weak (group I))	EML
13.4	Podophyllum resin	Podophyllotoxin	EML & EMLc
13.5	Benzyl benzoate	Precipitated sulfur topical ointment	EML & EMLc
14.1	Tropicamide	Atropine, cyclopentolate	EML & EMLc
15.1	Ethanol	Propanol	EML & EMLc
15.1	Povidone iodine	Iodine	EML& EMLc
15.2	Chlorine base compound	Remove square box, specify alternative formulations (powder, solid, liquid)	EML & EMLc
15.2	Chloroxylenol	Fourth level ATC chemical subgroup (D08AE Phenol and derivatives)	EML & EMLc
16	Furosemide	Fourth level ATC chemical subgroup (C03CA Sulfonamides, plain)	EML
16	Hydrochlorothiazide	Chlorothiazide, chlorthalidone, indapamide Chlorothiazide, chlorthalidone	EML EMLc
17	Pancreatic enzymes	Remove square box	EMLc
17.1	Omeprazole	Fourth level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	EML & EMLc
17.1	Ranitidine	Fourth level ATC chemical subgroup (A02BA H2-receptor antagonists) excluding combinations	EML & EMLc
17.2	Ondansetron	Dolasetron, granisetron, palonosetron, tropisetron	EML & EMLc

Table 1 *continued*

Updated square box listings			
Section	**Medicine**	**Specified therapeutic alternatives**	**List**
17.3	Sulfasalazine	Mesalazine	EML
17.3	Hydrocortisone	Remove square box for hydrocortisone retention enema. Add independent listing for prednisolone retention enema	EML
17.4	Senna	Bisacodyl	EML
18.4	Medroxyprogesterone acetate	Norethisterone	EML
18.5.2	Gliclazide	Fourth level ATC chemical subgroup (A10BB Sulfonylureas)	EML
21.1	Gentamicin	Amikacin, kanamycin, netilmicin, tobramycin	EML & EMLc
21.1	Ofloxacin	Fourth level ATC chemical subgroup (S01AE Fluoroquinolones)	EML & EMLc
21.1	Tetracycline	Chlortetracycline, oxytetracycline	EML & EMLc
21.3	Tetracaine	Fourth level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	EML & EMLc
21.4	Pilocarpine	Carbachol	EML
21.4	Timolol	Fourth level ATC chemical subgroup (S01ED Beta blocking agents) excluding combinations	EML
21.5	Atropine	Homatropine hydrobromide, cyclopentolate hydrochloride	EMLc
22.3	Ergometrine	Methylergometrine	EML
22.6	Ibuprofen	Indomethacin	EMLc
22.6	Prostaglandin E	Representative medicine prostaglandin E1, therapeutic alternative is prostaglandin E2	EMLc
24.2.1	Fluoxetine	Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline	EML
25.1	Beclometasone	Remove separate listing for beclometasone, consolidate with listing for budesonide	EML

Table 1 *continued*

Updated square box listings			
Section	**Medicine**	**Specified therapeutic alternatives**	**List**
25.1	Budesonide	Beclometasone, ciclesonide, flunisolide, fluticasone, mometasone	EML & EMLc
25.1	Budesonide + formoterol	Budesonide + salmeterol, beclometasone + formoterol, mometasone + formoterol, fluticasone + formoterol, fluticasone furoate + vilanterol	EML
25.1	Salbutamol	Terbutaline	EML & EMLc
25.1	Tiotropium	Aclidinium, glycopyrronium, umeclidinium	EML
26.2	Sodium lactate compound solution	Remove square box	EML & EMLc
27	Ergocalciferol	Colecalciferol	EML
27	Colecalciferol	Ergocalciferol	EMLc
27	Nicotinamide	Remove square box	EML
28	Ciprofloxacin	Ofloxacin	EMLc

Other changes to listings		
Abiraterone	Addition of a square box, indicating enzalutamide as a therapeutic alternative	EML
Amoxicillin	Remove indication for lower urinary tract infections	EML & EMLc
Bedaquiline	Change age limit from ≥ 6 years to ≥ 5 years	EML & EMLc
Benzathine benzylpenicillin	Correction of formulation description	EML & EMLc
Cefalexin	Change from second choice to first choice for skin and soft tissue infections	EML & EMLc
Efavirenz	Remove age/weight restriction as no longer included on EMLc for treatment of children	EML
Ethambutol	Replace tablet formulation strength range with specific strengths	EML
Isoniazid	Replace tablet formulation strength range with specific strengths	EML & EMLc

Table 1 *continued*

Other changes to listings		
Sodium fluoride	Transfer listing from Section 27 (Vitamins and Minerals) to the new section for dental preparations; amend the listing to "fluoride"; include toothpaste formulation and strength, with other formulations and strengths of topical fluoride preparations to be reviewed.	EML & EMLc
Valproic acid (sodium valproate)	Add note "avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb."	EML & EMLc

Changes to sections and subsections of the Model Lists		
	2019	**2021**
Section 6.1.4	N/A	Medicines for taeniid cestode cysts/ cysticidal medicines
Section 6.4.2.5	Medicines for prevention of HIV-related opportunistic infections	Fixed-dose combinations of antiretroviral medicines
Section 6.4.2.6	N/A	Medicines for prevention of HIV-related opportunistic infections
Section 15	Disinfectants and antiseptics	Antiseptics and disinfectants
Section 19.2	Sera and immunoglobulins	Sera, immunoglobulins and monoclonal antibodies
Section 29.2	Disease-modifying agents used in rheumatoid disorders (DMARDs)	Disease-modifying anti-rheumatic drugs (DMARDs)
Section 30	N/A	Dental preparations

Table 2
Applications and medicines not recommended for 2021 EML and EMLc

Additional medicines	
Addition of azacitidine for treatment of acute myeloid leukaemia	EML
Addition of anakinra for treatment of systemic onset juvenile idiopathic arthritis with macrophage activation syndrome	EML & EMLc
Addition of BRAF/MEK inhibitors for use in combination for the treatment of metastatic melanoma harbouring BRAFV600 mutation (dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib)	EML
Addition of cyclin-dependent kinase (CDK) 4/6 inhibitors for treatment of hormone receptor positive/HER2 negative advanced or metastatic breast cancer (abemaciclib, palbociclib, ribociclib)	EML
Addition of daratumumab for treatment of newly diagnosed and relapsed/refractory multiple myeloma	EML
Addition of fulvestrant for treatment of metastatic breast cancer	EML
Addition of hypochlorous acid solution for use in antisepsis and wound decontamination	EML & EMLc
Addition of methylphenidate for treatment of attention-deficit hyperactivity disorder	EML & EMLc
Addition of osimertinib for treatment of EGFR-mutation positive advanced non-small cell lung cancer	EML
Addition of PD-1/PD-L1 immune checkpoint inhibitors for treatment of locally advanced and metastatic non-small-cell lung cancer (atezolizumab, durvalumab, nivolumab, pembrolizumab)	EML
Addition of pertuzumab for treatment of HER2-positive unresectable or metastatic breast cancer	EML
Addition of tislelizumab for treatment of relapsed/refractory Hodgkin lymphoma	EML
Addition of tislelizumab for treatment of locally advanced or metastatic urothelial cancer	EML
Addition of tocilizumab for treatment of systemic onset juvenile idiopathic arthritis	EML & EMLc
Addition of triamcinolone hexacetonide for treatment of juvenile idiopathic arthritis	EML & EMLc
Addition of zanubrutinib for the treatment of relapsed/refractory chronic lymphocytic leukaemia	EML
Addition of zanubrutinib for the treatment of relapsed/refractory mantle cell lymphoma	EML

Table 2 *continued*

Additional formulations/strengths	
Injectable formulation of ethambutol for treatment of severe forms of tuberculosis	EML & EMLc
Injectable formulation of isoniazid for treatment of severe forms of tuberculosis	EML & EMLc
Injectable formulation of rifampicin for treatment of severe forms of tuberculosis	EML & EMLc
Fixed-dose combination of abacavir + lamivudine + lopinavir/ritonavir for treatment of HIV infection	EMLc
New indications	
New indication for N-acetylcysteine for management of non-paracetamol-induced acute liver failure	EML & EMLc
New indication for doxorubicin for treatment of rhabdomyosarcoma	EML & EMLc
New indication for simvastatin for treatment of polycystic ovary syndrome	EML
Deletions	
Deletion of formulations of antituberculosis medicines (ethambutol oral liquid 25 mg/mL; isoniazid oral liquid 50 mg/5 mL; pyrazinamide oral liquid 30 mg/mL; ethionamide tablet 125 mg)	EML & EMLc

List of participants

Expert Committee Members

Zeba Aziz, Professor of Medical Oncology, Rashid Latif Medical College, Lahore, Pakistan

Rita Banzi, Head of the Centre for Health Regulatory Policies, Mario Negri Institute, Milan, Italy (Rapporteur)

Graham Cooke, NIHR Research Professor of Infectious Diseases, Department of Infectious Disease, Imperial College, London, United Kingdom of Great Britain and Northern Ireland (Chair)

Elisabeth de Vries, Professor of Medical Oncology, University Medical Center, Groningen, the Netherlands (Vice-Chair)

Sumanth Gandra, Associate Professor, Division of Infectious Diseases, Washington University School of Medicine in St Louis, St Louis, United States of America

Myriam Khrouf, Professor of Pharmacology, Faculty of Pharmacy, University of Monastir, Monastir, Tunisia

Gilbert Kokwaro, Professor of Health Systems Research, Strathmore University, Nairobi, Kenya; Professor of Pharmaceutics, University of Nairobi, Nairobi, Kenya

Patrick Okwen, Primary care clinician, district medical officer and health economist, Bali, Cameroon

Gabriela Prutsky Lopez, Assistant Professor of Pediatrics, Mayo Clinic, Rochester, United States of America; co-founder of Unidad de Conocimiento y Evidencia (CONEVID), Universidad Peruana Cayetano Heredia, Lima, Peru

Rachel Riera, Medical rheumatologist, Associate Professor for Evidence-based Medicine, Universidade Federal de São Paulo, São Paulo, Brazil; coordinator of health technology assessment, Hospital Sírio-Libanês, São Paulo, Brazil

Andrew Roberts, Clinical haematologist, Royal Melbourne Hospital/Peter MacCallum Cancer Centre Melbourne, Australia; Professor and Cancer Theme Leader at the Walter & Eliza Hall Institute and the Metcalf Chair of Leukaemia Research, University of Melbourne, Melbourne, Australia

Mike Sharland, Professor of Paediatric Infectious Diseases, St George's University, London, United Kingdom

Shalini Sri Ranganathan, Professor in Pharmacology and specialist in Paediatrics, University of Colombo, Colombo, Sri Lanka

Fatima Suleman, Professor of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa; Director of the WHO Collaborating Centre for Pharmaceutical Policy and Evidence-Based Practice, Durban, South Africa

Ellen 't Hoen, Director of Medicines Law & Policy, founder and former executive director of the Medicines Patent Pool and a Global Health Law Fellow at the Faculty of Law, University of Groningen, Groningen, the Netherlands

Verna Vanderpuye, Clinical oncologist, senior consultant, National Center for Radiotherapy, Oncology and Nuclear Medicine, Korlebu Teaching Hospital, Accra, Ghana

Mei Zeng, Professor and Director, Department of Infectious Diseases and Chief, Infectious Diseases Unit, Children's Hospital of Fudan University, Shanghai, China

Temporary advisers

Andrea Biondi, Professor of Pediatrics and Director of the Pediatric Residency Program, University of Milano-Bicocca, Monza, Italy

Antonio Fojo, Professor of Medicine, Colombia University, New York, United States of America

Indah Widyahening, Associate Professor, Community Medicine Department, Universitas Indonesia, Jakarta, Indonesia

United Nations agencies

United Nations Children's Fund (UNICEF)

Akthem Fourati, Chief, Medicine & Nutrition Centre, UNICEF Supply Division, Copenhagen, Denmark

WHO regions

WHO Regional Office for Africa

Aissatou Sarassa, Technical Officer, Essential Drugs and Medicines, Ouagadougou, Burkina Faso

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Clive Ondari, Director, Department of Health Products Policy and Standards, Access to Medicines and Health Products

Declaration of interests for Expert Committee members and temporary advisers

WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflicts of interest. Declarations of interest and management of any disclosures is an important process governed by the WHO Guidelines for Declaration of Interests (WHO Experts).

Prior to being invited to participate in the 23rd meeting of the WHO Expert Committee on Selection and Use of Essential Medicines, all experts submitted written declarations of interest for consideration. In reviewing and assessing the declarations of interest, the WHO Essential Medicines List Secretariat sought the advice of the Office of Compliance, Risk Management and Ethics.

The declaration of interest process resulted in the participation of the Expert Committee Members and Temporary Advisers, as reported in the list of participants.

Experts who declared having no conflicts of interest were: Zeba Aziz, Sumanth Gandra, Gilbert Kokwaro, Patrick Okwen, Gabriela Prutsky-Lopez, Rachel Riera, Fatima Suleman, Verna Vanderpuye, Indah Widyahening and Mei Zeng.

The following experts disclosed interests, which were assessed by the Secretariat for actual or potential conflicts.

Rita Banzi disclosed that her research unit and institution has received research funding below the threshold of significant financial interest from Janssen Pharmaceuticals to support an educational programme for systematic review methodology. She also disclosed funding to her research unit and institution from AC.TA s.r.l. to support a series of ongoing investigator-initiated clinical trials on the use of hyperthermic intraperitoneal chemotherapy for the surgical treatment of different cancers. These disclosures were not considered to be related to the subject matter of the Expert Committee meeting and were determined not to represent a conflict.

Graham Cooke disclosed receiving payment below the threshold of significant financial interest for consultancy services from 30 Technology, a biotech company developing therapies using nitric oxide delivery. He also disclosed funding below the threshold of significant interest paid to his research unit for clinical trials involving remdesivir for COVID-19. These disclosures were not considered to be related to the subject matter of the Expert Committee meeting and were determined not to represent a conflict.

Elisabeth de Vries disclosed that she serves as an expert in data safety monitoring committees for trials promoted by a non-profit research programme (National Surgical Adjuvant Breast and Colon Project) and a for-profit company (Daiichi Sankyo). Trial sponsors provide funding to her institution (University Medical Center Groningen) to cover her time commitment. The matters under consideration by the data safety monitoring committees are unrelated to the medicines under evaluation by the Expert Committee.

She also disclosed that her institution is involved in early phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers. Her institution

receives research funding from Amgen, Bayer, CytomX, Crescendo Biologics, Genentech, G1 Therapeutics, Regeneron, Roche, Servier and Synthon. These trials are considered not to be directly related to medicines under evaluation by the Expert Committee.

She is a current member of the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) Working Group, having served as its Chair from 2013 to 2019. She is also Chair of the ESMO Cancer Medicines Committee. ESMO is a non-State actor in official relations with WHO. She is also co-Chair of the Response Evaluation Criteria in Solid Tumours (RECIST) Working Group, and Chair of the EML Cancer Medicines Working Group. All these positions are unpaid.

These disclosures were judged not to be directly related to the subject matter of the Expert Committee meeting and not to represent a conflict.

Myriam Khrouf disclosed having received personal remuneration below the threshold of significant financial interest for consultant and advisory services to pharmaceutical companies and clinical research organizations relating to generic drug development and bioequivalence studies, and as a board member of HOPIPHARM, the Association of Francophone Hospital Pharmacy. She also disclosed receiving financial research support from the British Society of Infectious Diseases, EUROQOL, Quality and Research Association and WHO for research into antimicrobial stewardship, health economics and outcomes research, and quality of life research. She also disclosed financial support from various pharmaceutical companies (Abbott, Merck, Novo Nordisk, Roche and Sanofi) and the Société Française de Pharmacie Oncologique for herself or her spouse for attendance at congresses, symposia and workshops, including travel and accommodation costs, registration fees and some remuneration. All amounts received were below the threshold of significant financial interest. These disclosures were judged to be non-significant and unrelated to the subject matter of the Expert Committee meeting, and were determined not to represent a conflict.

Ellen 't Hoen disclosed that she was the founding Director of the Medicines Patent Pool, a non-State actor in official relations with WHO. She remains a member of the expert advisory group of the Medicines Patent Pool. She disclosed having received grant funding from UNITAID to conduct a summary review on access to health products related to COVID-19. These disclosures were judged not to be directly related to the subject matter of the Expert Committee meeting and not to represent a conflict.

Andrew Roberts disclosed research support to his institution and/or research unit from pharmaceutical companies for investigator-initiated trials and laboratory research. AbbVie and Janssen Pharmaceuticals made donation of drugs (venetoclax and ibrutinib, respectively) for trials on mantle cell lymphoma. Servier provided financial support for laboratory-based research on B-cell lymphoma-2 inhibitors. This disclosure was considered non-significant and determined not to represent a conflict.

He also disclosed that he receives financial benefit from his employer, the Walter and Eliza Hall Institute (WEHI), in the form of a share of the income the Institute has received related to the drug venetoclax. Venetoclax was created during a partnership between the Walter and Eliza Hall Institute and the pharmaceutical companies AbbVie and Genentech. AbbVie and Genentech are

responsible for the commercial development of venetoclax. The Walter and Eliza Hall Institute has no role in its clinical trial development, commercialization or marketing. The Institute has a commercialization policy that allows distribution of a small share of any royalties and commercial income to staff who have invented or made a major contribution to the product. The amounts received by individual staff are based on specific criteria related to their contributions, and are not related to outcomes of clinical trials nor future drug sales. In 2017, the Walter and Eliza Hall Institute entered a commercial agreement with CPPIB Credit Europe S.à r.l., a wholly owned subsidiary of the Canada Pension Plan Investment Board, trading future venetoclax royalties for a lump-sum payment. He disclosed that he was a major contributor to research that lead to venetoclax and to early clinical trial discovery research, but is not a patent holder. His contributions predate the 2017 commercial agreement with the Canadian pension fund. For his contribution, he has been awarded a small fraction of this pension fund, which is diversified, independently managed and paid by his employer.

Venetoclax was not under evaluation by the Expert Committee at this meeting, but it can be used as an alternative to or in combination with ibrutinib. An application for ibrutinib was under evaluation by the Expert Committee for treatment of chronic lymphatic leukaemia. The EML Secretariat sought the guidance of the WHO Office for Compliance, Risk Management and Ethics in relation to the above-mentioned disclosure. An interest or interests that could directly influence, or could appear to influence, his professional judgement in relation to the subject matter of the Expert Committee meeting were not identified.

Mike Sharland disclosed that he is the Vice-Chair and Board Member of the Penta Foundation, an Italian charitable foundation that runs global trials to advance treatments for paediatric infectious diseases. These positions are unpaid. Penta collaborates with multiple pharmaceutical companies on the optimal design and conduct of observational and interventional trials of medicines. In his role with Penta, he has provided advice to pharmaceutical partners on improving the quality of the design and conduct of antibiotic trials in children, including to Shionogi & Co., Ltd for the design of paediatric trials of cefiderocol, an antibiotic under consideration by the Expert Committee in this meeting for use in adults. He has not provided advice nor had any discussions with pharmaceutical companies on antibiotic trials or studies in adults. He is Chair of the EML Antibiotics Working Group, an unpaid position. His disclosures were determined not to represent a conflict.

Shalini Sri Ranganathan disclosed that she received research funding below the threshold of significant financial interest from the Colombo University, where she is employed, to conduct a survey on availability and affordability of essential medicines for children in Sri Lanka, and to conduct a study on neonatal antibiotic use. These disclosures were considered non-significant and determined not to represent a conflict.

Temporary advisers

Andrea Biondi disclosed having received honoraria below the threshold of significant financial interest for his attendance at educational courses, symposia and advisory board meetings funded directly or through agencies by pharmaceutical companies (Amgen, Bluebird, Celgene-BMS, Incyte, Novartis, Takeda). He also disclosed having received honoraria for annual site visits to

Stichting Kinderen Kankervrij (KiKa Foundation) in the Netherlands, and for services rendered as a grant reviewer for the KiKa Foundation, Solving Kid's Cancer (United Kingdom), and Institut National du Cancer (France). He receives financial royalties from Oxford University Press for publication of the book *Cancer in Children: Clinical Management, 6th edition*, of which he was a co-editor. These disclosures were considered non-significant and determined not to represent a conflict.

He also disclosed that he served as co-principal investigator for a phase II trial of the tyrosine kinase inhibitor dasatinib in paediatric patients with Philadelphia chromosome positive acute lymphoblastic leukaemia. Dasatinib was not under evaluation by the Expert Committee at this meeting, but it can be used as an alternative to imatinib. An application for imatinib was under evaluation by the Expert Committee for this indication. This disclosure was considered non-significant and determined not to represent a conflict.

During the meeting, he disclosed that he is Scientific Director of the Fondazione Tettamanti, a not-for-profit research organization devoted to leukaemia and lymphoma research in children. The research units of Fondazione Tettamanti received financial support from competitive grants and from charities for research projects in the fields of genetics and immunotherapy of childhood leukaemia and lymphoma. The Fondazione has also filed a patent on a new technique for development of CAR-T cells. The research units of the Fondazione Tettamanti received research grants from CoImmune Inc., who acquired the licence for the above-mentioned CAR-T development technique, and that he personally received monetary support from CoImmune for consultancy services in relation to the CAR-T development technique. A review of the available evidence for CAR-T cell therapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma was submitted for consideration by the Expert Committee at this meeting; however, the review did not propose inclusion of CAR-T cell therapy on the EML at this time and a recommendation to list it was not requested. Nevertheless, this disclosure was judged to be significant and to represent an actual or ostensible conflict. After consultation with the WHO Office for Compliance, Risk Management and Ethics, it was determined that he could participate in the meeting as a temporary adviser, but that he should be excluded from the discussion related to the review of CAR-T cell therapy. He recused himself from the meeting while the review of CAR-T cell therapy was being discussed.

Antonio Fojo disclosed that he will be conducting a trial on a generic version of abiraterone for the treatment of prostate cancer in Veterans Administration Medical Centres. His research unit will receive research support and a donation of drugs from Sun Pharmaceutical Industries Limited. This activity is not associated with a direct salary or monetary support to him individually. Abiraterone may be used as an alternative to enzalutamide, a medicine under evaluation by the Expert Committee for metastatic prostate cancer at this meeting. This disclosure was considered non-significant and determined not to represent a conflict.

During the meeting, he disclosed that his spouse will be soon hired by Pfizer as a consultant, receiving direct salary support, to lead bioinformatics analyses of the PALOMA 3 clinical trial, a double-blind phase III study of palbociclib in metastatic breast cancer. Palbociclib is a medicine under evaluation at the present meeting, as part of the application for inclusion of cyclin-dependent kinase (CDK) 4/6 inhibitors on the EML. This disclosure was judged to be significant

and to represent an actual or ostensible conflict. After consultation with the WHO Office for Compliance, Risk Management and Ethics, it was determined that he could participate in the meeting as a temporary adviser, but that he should be excluded from the discussion, deliberation and decision-making related to the application for CDK 4/6 inhibitors. He recused himself from the meeting while the application for CDK 4/6 inhibitors was being discussed.

1. Introduction

The meeting of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines took place virtually and was hosted in Geneva, Switzerland, from 21 June to 2 July 2021. The aim of the meeting was to review and update the 21st WHO Model List of Essential Medicines (EML) and the 7th WHO Model List of Essential Medicines for Children (EMLc), the "Model Lists".

The meeting agenda included 88 applications involving over 100 medicines, medicine classes and formulations for addition, deletion, amendment and review in order to update the EML and EMLc.

The meeting was opened by Clive Ondari, Director, Health Products Policy and Standards Department, on behalf of WHO Director-General, Dr Tedros Adhanom Ghebreysus. Dr Ondari welcomed Committee members and temporary advisers, representatives from WHO regional offices and other UN agencies.

In his opening remarks, Dr Ondari highlighted that access to essential medicines remains a top priority, particularly during the COVID-19 pandemic, with medicines proven to be effective for the treatment of COVID-19 (oxygen and dexamethasone) included on the Model Lists for over 40 years. Unfortunately, the pandemic has also illustrated that access to some essential medicines remains a problem in many settings. He described some of the opportunities to improve access to essential medicines, including WHO prequalification, increased use of biosimilar medicines and expansion of the work of the Medicines Patent Pool.

Dr Ondari drew attention to the large number of applications for cancer medicines for consideration by the Committee, which comprised 40% of all applications for new medicines on the agenda. In addition, he noted that the high price and complex infrastructure required to use some of these proposed medicines appropriately are significant barriers to access, and requested the Committee advise WHO which, if any, of these medicines should be considered essential, despite the high prices.

The Access–Watch–Reserve (AWaRe) classification of antibiotics was also highlighted. First proposed by the Committee in 2017, this classification has gained widespread support as a tool to ensure access to essential antibiotics, and for guiding antibiotic stewardship. An update of the AWaRe classification, proposed by members of the EML Antibiotics Working Group, will be reviewed by the Committee. The EML Antibiotics Working Group have also developed a complementary tool – the WHO EML antibiotic book – to support the appropriate use of antibiotics and achievement of the target that 60% of antibiotic consumption should come from the Access category by 2023. This book will provide up-to-date, evidence-based guidance on the management of over 35 infectious syndromes, including first- and second-choice

antibiotics to use and when no antibiotics are needed, and is aligned with the recommendations in the Model Lists and AWaRe.

Dr Mariângela Simão, Assistant Director-General, Access to Medicines and Health Products, also addressed the Committee, and presented an overview of the division's programme covering diabetes and reiterated WHO's commitment to improve access to diabetes therapies. She advised that a comprehensive strategy for access to insulin and other medicines for diabetes needs to include not only the medicines but also devices for administration and blood sugar measurement. She reported that efforts made by WHO to encourage manufacturers to invest in quality-assured human insulin through the prequalification programme had not been successful in prequalifying any human insulin products. She noted that applications for insulin analogues and sodium–glucose transport protein 2 (SGLT2) inhibitors are once again before the Committee for consideration, having not been recommended on multiple occasions in the past. Dr Simão recognized the challenge of capturing the benefits of therapeutic innovation while managing the accompanying financial burden, and the importance of better negotiation in addressing this challenge. Creating transparency on what fair pricing for essential medicines constitutes will be an important step to help countries increase the number of people that can benefit from important medicines and make progress towards universal health coverage. With reference to the applications before the Committee for smoking cessation medicines, she also highlighted reports of increased tobacco use in some countries as a result of the COVID-19 pandemic and associated stress, and how evidence has confirmed that current and former smokers are at greater risk of severe COVID-19 infection.

Dr Simão reminded Committee members and temporary advisers of their obligation to provide advice to WHO in their individual capacities as experts, and not as representatives of their governments, institutions or organizations. She acknowledged the considerable work already undertaken by members and temporary advisers in reviewing applications and thanked them for the time they had spent in preparation, as well as for dedicating their time over the coming weeks of the meeting to contribute to and support the WHO's work.

2. Open session

The open session of the meeting was held virtually and was chaired by Benedikt Huttner, Secretary of the Expert Committee. It was attended by a variety of interested parties including representatives of WHO Member States, nongovernmental organizations, academia and civil society.

Updates from the WHO Secretariat were presented by Dr Huttner and Francis Moussy, Secretary of the Strategic Advisory Group of Experts for Essential In Vitro Diagnostics.

Chairs of the EML Working Groups for antibiotics (Mike Sharland) and cancer medicines (Elisabeth de Vries) presented updates of the work undertaken by the respective working groups since the last Expert Committee meeting.

Navindra Persaud, Associate Professor at the University Toronto, Canada, presented findings from the CLEAN Meds randomized control trial which evaluated the impact of providing selected essential medicines free of charge to primary care patients on treatment adherence, care costs and well-being.

Christopher Booth, Professor of Oncology at Queen's University Cancer Research Institute, Kingston, Canada, presented results from a survey of front-line oncologists on availability of and access to essential cancer medicines.

Daniela Garone, International Medical Coordinator at Médecins Sans Frontières, gave a presentation on the role of essential medicines in emergency and humanitarian settings.

Additional presentations and/or statements were made by the following participants:

- Nine Steensma, Clinton Health Access Initiative
- Rosa Giuliani, European Society for Medical Oncology
- Hans Hogerzeil, Groningen University
- Margaret Ewen, Health Action International
- Ayesha Sitlani, International AIDS Vaccine Initiative and Wellcome
- Sara Amini, International Federation of Pharmaceutical Manufacturers and Associates
- John Wiernikowski, International Society of Oncology Pharmacy Practitioners
- Kavian Kulasabanathan, Knowledge Ecology International
- Esteban Burrone, Medicines Patent Pool

- Katherine Souris, T1 International
- Neelu Paleti, Universities Allied for Essential Medicines

Copies of all presentations and statements are available on the WHO website[2].

[2] https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee

3. General items

Highly priced medicines

Throughout the meeting, the Expert Committee noted the trend of continual increases in prices of new medicines over time, particularly for cancer, autoimmune diseases, infectious diseases and rare diseases. Among new highly priced medicines, few offer additional relevant benefits sufficient to reach the status of essential medicines. For instance, in cancer, only a minority of all the medicines approved by the United States Food and Drug Administration and the European Medicines Agency over the past 2 decades have reached undisputable results of prolonging survival by 4–6 months, a guiding criterion for a cancer medicine to be considered for addition on the EML (*1–4*). Nevertheless, some of these medicines are associated with large, clinically relevant benefits and favourable safety profiles, yet their prohibitively high price – multiples of median annual household incomes making them unaffordable even in high-income countries – has delayed or prevented the Committee from recommending their inclusion on the Model Lists. The problem of affordability is not only limited to new medicines, as some "old" highly effective medicines, such as insulins, are also often priced at a level that represents a major barrier to access given the need for chronic, sometimes lifelong, treatment.

The Committee recognized the ongoing challenge of making such medicines more affordable for the people and communities who need to access them. For low- and middle-income countries, this is especially important given that the number of people living with diseases that may require these medicines is steadily increasing. Coverage of high-priced medicines requires national budget surpluses that are unlikely to be available for decades, even in emerging market economies. Therefore, it is likely that availability of these medicines without reimbursement policies will increase disparities between patients living in the same country. Alternatively, countries might increase their budget deficit, which would have negative implications for their national or regional debt.

The Committee noted the increasing tension between the desire to include medicines in the EML that show major benefits and the concerns about budget implications for countries if these medicines are eventually listed. The class of medicines that best represents this state of tension is the immune checkpoint inhibitors for treatment of lung cancer, which are prohibitively expensive even in countries with advanced economies and strong financial negotiation power.

The Committee recommended establishing a standing EML Working Group to support the Committee to provide advice to WHO on policies and rules to make highly priced essential medicines more affordable and accessible. Tasks of the Working Group should include:

- exploration of thresholds at which specific essential medicines become affordable in relation to countries' and patients' ability to pay;
- identification of prices that represent "fair value" for the benefits expected from essential medicines;
- identification of interventions by policy-makers and other actors that could facilitate relevant and rapid decreases in prices to reach universal access to these treatments; and
- development of a strategy to monitor price and availability trends of essential but unaffordable medicines, to be proposed as part of the next WHO General Programme of Work.

The Committee highlighted that price barriers may require a more granular and focused approach. High-level recommendations on pharmaceutical pricing policies (e.g. use of external reference pricing) might identify broad interventions to address price inflation at country level. However, it might be difficult to foresee the implications of such policies for single medicines or classes. The Committee suggested WHO investigate innovative targeted price policy actions which governments can take to control prices of single essential medicines or classes, such as insulins or immune checkpoint inhibitors, in which price represents a major obstacle to access. Equity, greater equality of access and affordability should be main pillars of any proposed solutions.

The Working Group should collaborate closely with groups within WHO and other external stakeholders working to increase affordability and transparency of prices and costs of health products.

The Committee reiterated the important role of the Medicines Patent Pool in facilitating affordable access to essential medicines through negotiation of public health-oriented licences with patent holders to allow generic manufacture and supply of medicines in low- and middle-income countries. The Committee welcomed the expansion of the Medicines Patent Pool's mandate to patented essential medicines beyond HIV, hepatitis C and tuberculosis, to include other small molecules included in the Model Lists, and medicines with strong potential for future inclusion. Among the new medicines recommended for inclusion on the Model Lists at this meeting, the Committee requested that the Medicines Patent Pool explore licensing possibilities for enzalutamide, ibrutinib and the sodium–glucose transport protein 2 inhibitors. A number of patented medicines were not recommended for inclusion on the Model Lists at this meeting, either because they were considered not to be cost-effective at current prices, or because the available evidence was promising but not yet sufficiently mature. However, the Committee considered that cyclin-dependent kinase (CDK) 4/6 inhibitors, daratumumab, osimertinib, PD 1/PD-L1 immune

checkpoint inhibitors and zanubrutinib all had potential for future inclusion and recommended the Medicines Patent Pool explore the application of its licensing model to these medicines.

References

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3. Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. JAMA Intern Med. 2019;179(7):906–13.
4. Ladanie A, Schmitt AM, Speich B, Naudet F, Agarwal A, Pereira TV, et al. clinical trial evidence supporting US Food and Drug Administration approval of novel cancer therapies between 2000 and 2016. JAMA Netw Open. 2020;3(11):e2024406.

Switching between originator and similar biological products

The Expert Committee noted that the introduction of biological medicines (or biotherapeutic products) into clinical use has markedly improved outcomes for many serious and rare conditions that were previously difficult to treat. Biological medicines are often highly priced, limiting access in many settings. Similar biological products (biosimilars) are biological medicines that are highly similar in terms of quality, safety and efficacy to an already licensed biological product. Over the past few years, the expiry of patents and/or other data protection certificates of biological medicines has fueled interest in increasing the availability of biosimilars since they have the potential to improve access to safe and effective biological medicines by reducing prices through competition.

Since biological products are often large and complex proteins, they are more complicated to produce than small molecules and difficult to copy exactly. Biosimilars may therefore differ slightly in the structure from the originator product (e.g. the degree of glycosylation), thus requiring a different regulatory framework for licensing than for generics of small molecules. Although the exact criteria for biosimilarity differ among countries and regions, regulatory authorities approve biosimilars based on the assessment of quality and structural, functional, preclinical and clinical similarity with respect to the originator. Approved biosimilars are expected to produce the same clinical results as the originator product. Therefore, regulatory authorities do not usually require specific studies assessing if alternating between the biosimilar and its originator or switching from the biosimilar to its originator affect safety and/or efficacy. It is important to note that changes in the manufacturing process (and hence the structure) of biological medicines are common and that it therefore can be

assumed that the risk of switching from an originator to a biosimilar is similar to switching between two batches of any biologic medicines.

The Committee acknowledged that there is an intense debate on the interchangeability of originator and biosimilar products. Policies on interchangeability (both substitution and switching) of biological medicines and their biosimilars vary across settings. However, these policies are often restrictive in nature, and countries face limitations in choice of potential alternatives, and possibly a reduction in access to affordable medicines. This concerns especially "substitutions", i.e. the replacement of one product for another at the pharmacy level, or "non-medical switches", i.e. switching treatment in patients for non-clinical reasons, such as cost or procurement issues. Several professional societies and patient groups strongly advocate that any decision to exchange an originator with a biosimilar should remain the responsibility of the physicians in consultation with their patients. Most high-income countries do not allow substitution at the pharmacy level, but rather encourage physicians to prescribe the best-value treatment possible, which often means substituting the originator with a biosimilar. Several low- and middle-income countries facing financial constraints have implemented substitution practices without apparent major detrimental effects on the efficacy or safety of treatments.

The Committee noted that there is a need to increase physicians' and patients' confidence in biosimilar medicines and suggested that regulators and health authorities should promote policies on biosimilar interchangeability. Active postmarketing surveillance of adverse events associated with switching to biosimilar products should be assured. In addition to data supporting biosimilarity at the time of approval, these data should reassure prescribers about interchangeability.

The Committee considered the reports submitted of the available evidence for switching between originator and biosimilar products for antitumour necrosis factor (TNF) biologicals, erythropoietins and insulins. The Committee noted that a substantial body of evidence exists that switching from originator to biosimilar products of anti-TNF medicines does not affect safety, immunogenicity and efficacy in a variety of conditions. More limited evidence suggests similar conclusions for erythropoietins and insulin analogues. Differences in discontinuation rates in open-label studies comparing originators with biosimilars are often driven by the so-called nocebo effect due to patients' negative expectations of biosimilars and not the pharmacological action of the medicine itself.

The Committee considered that reducing uncertainties about the use of biosimilars and supporting strategies promoting interchangeability at the procurement and clinical level have a great potential to increase global access to effective biological medicines. For the biological medicines included on the

Model Lists, the Committee recommended that quality-assured biosimilars should be considered interchangeable and eligible for selection and procurement at the country level for national essential medicines lists (see also Review of "square box" listings below). These recommendations, together with other guidance provided by WHO promoting the use of quality-assured generic and biosimilar medicines (*1*), will support countries in making evidence-based, timely and informed choices when considering the inclusion of biological medicines and biosimilars on their national lists.

References

1. WHO guideline on country pharmaceutical pricing policies. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/335692).

Review of square box listings

The Expert Committee noted that the square box symbol is intended to indicate similar clinical performance of different medicines within a pharmacological class, and that suitable therapeutic alternatives may be considered for selection at the country level for national essential medicines lists. The Committee recognized that considerable heterogeneity exists in the Model Lists with the use and application of both the square box symbol and other ad hoc notes intended to indicate acceptable therapeutic alternatives.

To provide greater clarity for national EML selection committees, the Committee recommended that the square box listing concept should be used consistently and exclusively, replacing notes where they exist. In addition, square box listings should be qualified to explicitly indicate the recommended therapeutic alternatives. These may be individual medicines, or multiple medicines within a pharmacological class or therapeutic subgroup, defined at the fourth level of the Anatomical Therapeutic Chemical (ATC) classification.

For biological medicines on the Model Lists, the Committee considered that quality-assured biosimilars are appropriate therapeutic alternatives for selection at the country level. However, in the same way that the square box is not used to indicate alternative generic brands of the same small molecule medicines, the square box should not be used to indicate alternative quality-assured biosimilars of biological medicines. Nevertheless, the Committee recognized that greater availability of biosimilar medicines could lead to greater market competition, improved access to medicines and reduced costs to both patients and health systems. To support the uptake of quality-assured biosimilars at the country level, the Committee recommended that listings for biological medicines on the Model Lists should include a separate note specifying that quality-assured biosimilars are appropriate for selection.

The Committee endorsed the proposals made by the Secretariat for amendments and reviews of the current square box listings, with the following exceptions.

- An independent listing for erythromycin on the EMLc as a second-choice treatment for pharyngitis was not recommended. Instead, a square box was added to the listing for clarithromycin, indicating erythromycin as an alternative.
- A review of ophthalmological anti-inflammatory medicines was recommended before any changes are made to the square box listing for prednisolone eye drops on the EML and EMLc.
- A review of the square box listing for amlodipine as an antihypertensive medicine on the EML was not recommended. Alternatives should be dihydropyridine calcium channel blockers, defined at the fourth level ATC classification.
- For the listing of prostaglandin E on the EMLc, it was recommended to retain the square box but assign it to prostaglandin E1, and specify prostaglandin E2 as an alternative.

Refer to Table 1 of the Executive Summary for details of the updated square box listings.

Update to the AWaRe classification of antibiotics

The Expert Committee acknowledged the contributions of the EML Antibiotics Working Group and endorsed the Working Group's recommendations for the update of the AWaRe classification of antibiotics. An additional 81 antibiotics were classified (40 as Access, 34 as Watch and seven as Reserve) and will be included in the 2021 update of the AWaRe classification database, to support stewardship and monitoring of antibiotic use.

The Committee also noted the request from the WHO Department of Global Coordination and Partnership (Antimicrobial Resistance Division) for a comprehensive review of the Reserve group currently included on the Model Lists, as well as newly approved Reserve group antibiotics. The Committee agreed that providing more focused guidance for WHO Member States on which Reserve antibiotics should be considered essential from a public health perspective and included in national access programmes would be beneficial. The Committee therefore requested the Secretariat and the EML Antibiotics Working Group to undertake this review for consideration by the Committee at the next meeting.

Disease-modifying therapies for multiple sclerosis – update

In 2019, the WHO Expert Committee provided feedback on the application by the Multiple Sclerosis International Federation to add the disease-modifying therapies glatiramer acetate, fingolimod and ocrelizumab to the Model Lists for treatment of multiple sclerosis. Feedback given by the 2019 Expert Committee included the need to review commonly used disease-modifying therapies that were not, or were only partly, reviewed in the original application, such as azathioprine, natalizumab and rituximab. Furthermore, it was noted that the superiority of the disease-modifying therapies included in the application over other therapeutic options with regard to benefits, harms and affordability did not clearly emerge. The 2021 Expert Committee acknowledged the update by the Multiple Sclerosis International Federation that a revised application addressing the issues outlined above would be submitted in 2022, for evaluation by the Committee for the update of the Model Lists in 2023.

Comprehensive review of essential medicines for mental health conditions

The Expert Committee welcomed and supported the proposal from the WHO Department of Mental Health and Substance Use for a comprehensive review of the mental health chapters of the EML and EMLc to be carried out in the next biennium, to ensure that the Model Lists are updated and consistent with recommendations in WHO guidelines for the management of mental health disorders. The Committee agreed that providing more focused guidance for WHO Member States on which medicines for mental health conditions should be considered essential from a public health perspective and included in national access programmes would be beneficial.

Therapeutic drug monitoring – advice for SAGE-IVD

The Expert Committee considered a report and request for advice from the Secretary of the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE-IVD). The SAGE-IVD requested the Committee's endorsement or modification of a prioritized list of essential medicines for which therapeutic drug monitoring is required. This would then inform a call for submissions for relevant in vitro diagnostic tests for therapeutic drug monitoring to be evaluated for inclusion on the WHO Model List of Essential In Vitro Diagnostics.

The Expert Committee advised that it considered the proposed prioritized list of medicines to be appropriate, with the exception of methotrexate. Because the use of methotrexate is common in clinical practice for several diseases, the Committee recommended that therapeutic drug monitoring of methotrexate be

considered a high priority to reduce the incidence of toxicity, especially when methotrexate is used in high-dose treatment protocols.

Following recommendations made at the meeting for the inclusion of everolimus and tacrolimus on the Model Lists, the Committee also advised that these medicines be considered as moderate priority candidates for therapeutic drug monitoring assays. In addition, the Committee considered that there is a role for therapeutic drug monitoring of voriconazole in *Aspergillus* infections due to its pharmacokinetic characteristics and potential for drug–drug interactions. Therefore, the Committee advised that voriconazole be considered a moderate priority candidate for therapeutic drug monitoring assays.

4. Summary of recommendations

Changes to Sections of the Model Lists

Refer to Table 1 of the Executive Summary for details of changes to sections and subsections of the Model Lists.

Additions to the Model Lists

Section 6.2.1: Trimethoprim was added to the core list of the EML and EMLc as an Access group antibiotic for treatment of lower urinary tract infections.

Section 6.2.3: Cefiderocol was added to the complementary list of the EML as a Reserve group antibiotic for treatment of infections due to multidrug-resistant organisms.

Section 6.3: Micafungin, with a square box, was added to the complementary list of the EML and EMLc for the treatment of invasive candida infections. Therapeutic alternatives under the square box listing are anidulafungin and caspofungin.

Section 6.4.4.2.1: Daclatasvir, daclatasvir + sofosbuvir, glecaprevir + pibrentasvir, sofosbuvir and sofosbuvir + velpatasvir were added to the core list of the EMLc as pan-genotypic treatment for children with chronic hepatitis C virus infection.

Section 7.1: Sumatriptan was added to the core list of the EML for the treatment of acute migraine.

Section 8.1: Tacrolimus was added to the complementary list of the EML and EMLc for the prevention and treatment of graft rejection following organ transplantation.

Section 8.2.1: Vinorelbine was added to the complementary list of the EMLc for the treatment of rhabdomyosarcoma.

Section 8.2.2: Everolimus was added to the complementary list of the EML and EMLc for the treatment of subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Ibrutinib was added to the complementary list of the EML for the treatment of relapsed/refractory chronic lymphocytic leukaemia.

Section 8.2.5: Rasburicase was added to the complementary list of the EML and EMLc for the treatment and prevention of tumour lysis syndrome.

Section 13.4: Calcipotriol, with a square box, was added to the core list of the EML and EMLc for the treatment of psoriasis. Therapeutic alternatives under the square box listing are calcitriol and tacalcitol.

Section 18.5.1: Long-acting insulin analogues, with a square box, were added to the core list of the EML and EMLc for the treatment of types 1 and 2 diabetes in patients at high risk of hypoglycaemia. Therapeutic alternatives under the square box listing are insulin degludec, insulin detemir and insulin glargine, including quality-assured biosimilar products.

Section 18.5.2: Empagliflozin, with a square box, was added to the core list of the EML for the treatment of adults with type 2 diabetes with or at high risk of cardiovascular disease or diabetic neuropathy. Therapeutic alternatives under the square box listing are canagliflozin and dapagliflozin.

Section 19.2: Anti-rabies virus monoclonal antibodies and equine rabies immunoglobulin were added to the core list of the EML and EMLc for rabies postexposure prophylaxis.

Section 22.5: Multiple micronutrient supplement was added to the core list of the EML for use as an antenatal supplement.

Section 24.1: Paliperidone long-acting injection, with a square box, was added to the core list of the EML for the treatment of schizophrenia and related chronic psychotic disorders. A therapeutic alternative under the square box listing is risperidone long-acting injection.

Section 24.5: Bupropion and varenicline were added to the core list of the EML for use in smoking cessation.

Section 29.2: Hydroxychloroquine was added to the complementary list of the EML for the treatment of cutaneous lupus erythematosus and systemic lupus erythematosus.

Section 30: Glass ionomer cement and silver diamine fluoride were added to the core list of the EML and EMLc for the prevention and treatment of dental caries. The listing for sodium fluoride was transferred from Section 27, and amended to fluoride, to accommodate listing for fluoride toothpaste and other topical fluoride-containing preparations for the prevention and treatment of dental caries.

Deletions from the Model Lists

Section 6.2.5: Amikacin 100 mg, 500 mg and 1 g powder for injection, isoniazid 50 mg scored tablet, linezolid 400 mg tablet and 2 mg/mL intravenous injection, p-aminosalicylic acid 500 mg tablet, and pyrazinamide 150 mg scored tablet formulations were deleted from the EML and EMLc. Isoniazid + pyrazinamide + rifampicin 75 mg + 400 mg + 150 mg tablets were deleted from the EML.

Amoxicillin + clavulanic acid 125 mg + 31.25 mg powder for oral liquid was deleted from the EMLc.

Section 6.4.2: Atazanavir 100 mg solid oral dosage form, efavirenz 200 mg scored tablet, lopinavir + ritonavir 400 mg + 100 mg/5 mL oral liquid, raltegravir 100 mg chewable tablets, and ritonavir 400 mg/5 mL oral liquid were deleted from the EML and EMLc. Atazanavir 300 mg solid oral dosage form and lamivudine + nevirapine + zidovudine 150 mg + 200 mg + 300 mg were deleted from the EML. Abacavir 60 mg dispersible tablets, lamivudine 150 mg tablets, lamivudine + nevirapine + zidovudine 30 mg + 50 mg + 60 mg tablets, raltegravir 400 mg tablets and ritonavir 100 mg oral powder were deleted from the EMLc.

Section 6.4.3: Oseltamivir 12 mg/mL powder for oral liquid was deleted from the EML and EMLc.

New indications

Section 6.1.4: New indications of diseases caused by taeniid cestode cysts (cystic echinococcosis, alveolar echinococcosis and neurocysticercosis) were added for albendazole, mebendazole and praziquantel on the EML and EMLc.

Sections 6.2.1 and 6.2.2: Additional indications for Access and Watch group antibiotics were included in the EML and EMLc as follows:

- Endophthalmitis (EML and EMLc): ceftazidime, ceftriaxone, vancomycin
- Necrotizing fasciitis (EML and EMLc): ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam, vancomycin
- Complicated intraabdominal infections (EMLc): ampicillin, gentamicin
- Neonatal meningitis (EMLc): gentamicin.

Section 6.2.5: The new indication for treatment of drug-susceptible tuberculosis was included for moxifloxacin and rifapentine on the EML.

Section 8.2: Additional indications for antineoplastic and supportive medicines were included in the EML and EMLc as follows:

- Acute myeloid leukaemia: etoposide
- Burkitt lymphoma: dexamethasone, hydrocortisone, ifosfamide, mesna, methotrexate, methylprednisolone
- Ewing sarcoma: dactinomycin
- Head and neck cancer (EML only): carboplatin (as a radiosensitizer)

- Low-grade glioma: carboplatin, cisplatin, cyclophosphamide, vinblastine, vincristine
- Nephroblastoma: carboplatin, cyclophosphamide, etoposide, ifosfamide, irinotecan, mesna
- Ovarian germ cell tumours: carboplatin
- Osteosarcoma: etoposide
- Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia: imatinib
- Rhabdomyosarcoma: irinotecan, vinorelbine
- Testicular germ cell tumours: carboplatin

Section 21.1: The new indication of bacterial conjunctivitis was included for ofloxacin eye drops on the EML and EMLc.

New formulations/strengths

Sections 6.2.1 and 6.2.2: Additional formulations and/or strengths of the following Access and Watch group antibiotics were included on the EML:

- Amoxicillin: solid oral dosage form 1 g
- Amoxicillin + clavulanic acid: tablet 875 mg + 125 mg
- Cefalexin: solid oral dosage form 500 mg
- Ceftriaxone: powder for injection 2 g
- Ciprofloxacin: solid oral dosage form 500 mg
- Clindamycin: injection 600 mg/4 mL, 900 mg/6 mL
- Phenoxymethylpenicillin: tablet 500 mg
- Vancomycin: powder for injection 500 mg, 1 g

Section 6.2.5: Additional formulations and strengths of the following medicines for the treatment of tuberculosis were included:

- Amikacin (EML and EMLc): injection 100 mg/2 mL, 250 mg/mL in 2 mL vial
- Bedaquiline (EMLc): tablet 20 mg
- Delamanid (EMLc): tablet (dispersible) 25 mg
- Isoniazid + rifapentine (EML and EMLc): tablet 300 mg + 300 mg
- Pyrazinamide (EML and EMLc): tablet 500 mg
- Rifapentine (EML and EMLc): tablet 300 mg

Section 6.4.2.4: A 10 mg dispersible, scored tablet formulation of dolutegravir was included in the EMLc for the treatment of HIV in children.

Section 6.4.4.2.1: Sofosbuvir 200 mg tablets and a fixed dose combination tablet of daclatasvir + sofosbuvir 60 mg + 400 mg were included in the EML for the treatment of chronic hepatitis C virus infection.

Section 8.2.1: Additional formulations and strengths of the following cancer medicines were included:

- Cisplatin (EML and EMLc): injection 10 mg/10 mL, 20 mg/20 mL
- Cyclophosphamide (EML and EMLc): powder for injection 1 g, 2 g in vial
- Vinblastine (EML and EMLc): injection 10 mg (sulfate)/10 mL
- Vincristine (EML and EMLc): injection 1 mg (sulfate)/mL, 2 mg (sulfate)/2 mL
- Vinorelbine (EML): capsule 20 mg, 30 mg, 80 mg

Section 17.3: Prednisolone retention enema formulation 20 mg/100 mL (as sodium phosphate) was included in the EML for the treatment of Crohn disease and ulcerative colitis.

Section 22.1.6: A combined contraceptive vaginal-ring formulation of ethinylestradiol + etonogestrel was included in the EML.

Other changes to listings

Sections 5 and 24.2.2: Addition of cautionary note on the use in pregnancy and in women and girls of child-bearing potential to the listings for valproic acid (sodium valproate) on the EML and EMLc.

Section 6.2.1: Removal of the indication for lower urinary tract infection from the listing of amoxicillin on the EML and EMLc. Change to the listing for cefalexin on the EML and EMLc from second choice to first choice for skin and soft tissue infections.

Section 6.2.5: Change to the age limit for bedaquiline from ≥ 6 years to ≥ 5 years. Replacement of formulation strength ranges with specific formulation strengths for ethambutol and isoniazid.

Section 6.4.2.2: Removal of the age and weight limit for efavirenz on the EML as efavirenz is no longer included on the EMLc for treatment of children with HIV.

Section 8.2.4: Addition of a square box to the listing of abiraterone on the EML, specifying enzalutamide as a therapeutic alternative.

Section 27: Transfer of the listing of sodium fluoride from Section 27 (Vitamins and Minerals) to the new section (Section 30) for dental preparations; amendment of the listing to "fluoride"; inclusion of toothpaste formulation and strength, with other formulations and strengths of topical fluoride preparations to be reviewed.

Refer to Table 1 of the Executive Summary for details of changes made following the review of square box listings on the Model Lists.

Applications not recommended

Section 4.2: New indication of non-paracetamol-induced acute liver failure for N-acetylcysteine (EML and EMLc).

Section 6.2.5: Inclusion of intravenous formulations of ethambutol, isoniazid and rifampicin for severe forms of tuberculosis (EML and EMLc). Deletion of oral liquid formulations of ethambutol, isoniazid and pyrazinamide, and 125 mg tablet formulation of ethionamide.

Section 6.4.2.5: Inclusion of a fixed-dose combination formulation of abacavir + lamivudine + lopinavir/ritonavir for HIV infection in children (EMLc).

Section 8.2: Applications for the following cancer medicines:

- Inclusion of azacitidine for acute myeloid leukaemia (EML)
- Inclusion of BRAF/MEK inhibitors (dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib) for metastatic melanoma with BRAFV600 mutation (EML)
- Inclusion of cyclin-dependent kinase (CDK) 4/6 inhibitors (abemaciclib, palbociclib, ribociclib) for hormone receptor positive/HER-2 negative advanced or metastatic breast cancer (EML)
- Inclusion of daratumumab for newly diagnosed and relapsed/refractory multiple myeloma (EML)
- Inclusion of fulvestrant for metastatic breast cancer (EML)
- Inclusion of osimertinib for EGFR mutation-positive advanced non-small-cell lung cancer (EML)
- Inclusion of PD-1/PD-L1 immune checkpoint inhibitors (atezolizumab, durvalumab, nivolumab, pembrolizumab) for locally advanced and metastatic non-small-cell lung cancer (EML)
- Inclusion of pertuzumab for HER-2 positive unresectable or metastatic breast cancer (EML)

- Inclusion of tislelizumab for relapsed/refractory Hodgkin lymphoma and locally advanced or metastatic urothelial cancer (EML)
- Inclusion of zanubrutinib for relapsed/refractory chronic lymphocytic leukaemia and relapsed/refractory mantle cell lymphoma (EML)
- New indication of rhabdomyosarcoma for doxorubicin (EML and EMLc)

Section 15: Inclusion of hypochlorous acid solution for use in antisepsis and wound decontamination (EML and EMLc).

Section 22: New indication of polycystic ovary syndrome for simvastatin (EML).

Section 24: Inclusion of methylphenidate for attention-deficit hyperactivity disorder (EML and EMLc).

Section 29.3: Inclusion of the following medicines for juvenile joint diseases on the EML and EMLc:

- Anakinra for systemic onset juvenile idiopathic arthritis with macrophage activation syndrome
- Tocilizumab for systemic onset juvenile idiopathic arthritis
- Triamcinolone hexacetonide for juvenile idiopathic arthritis

5. Applications for the 22nd Model List of Essential Medicines and the 8th Model List of Essential Medicines for Children

Section 4: ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS

4.2 Specific

N-acetylcysteine – addition – EML and EMLc

N-acetylcysteine **ATC Code: V03AB23**

Proposal

Addition of N-acetylcysteine on the EML and EMLc for a new indication for the management of non-paracetamol-induced acute liver failure caused by etiologies that deplete glutathione.

Applicant

Jill M. Pulley, Rebecca Jerome; Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University Medical Center, Nashville, United States of America

WHO technical department

Comments were received from the WHO Department of Neglected Tropical Diseases. The technical department advised that the evidence presented in the application for incorporation of N-acetylcysteine for treatment of dengue-associated liver injury or failure is based on incomplete reports. Further studies are needed to strengthen the evidence. It must be very clear that including N-acetylcysteine as an essential medicine does not represent a recommendation for its use in dengue-induced liver failure.

The technical department had no objection to including N-acetylcysteine as an essential medicine for liver failure in general, if there are sufficient data in the application.

EML/EMLc

EML and EMLc

Section

4.2 Antidotes and other substances used in poisonings – Specific

Dose form(s) & strength(s)

Injection: 200 mg/mL in 10 mL ampoule
Oral liquid: 10%, 20%

Core/Complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Acetylcysteine injection was added to the EML in 1999 and to the EMLc in 2007 for the treatment of paracetamol poisoning. The oral formulation was added in 2009.

Public health relevance (burden of disease)

Acute liver failure is a serious clinical condition, with high morbidity and mortality in the absence of supportive clinical care and potentially liver transplantation (*1*, *2*). It affects all age groups, and there are many causes. This application focuses on acute liver failure with known involvement of glutathione, since this protein is targeted by N-acetylcysteine.

Acute viral hepatitis infections are responsible for most cases of acute liver failure globally, with variation in causative viral pathogen in different regions (e.g. hepatitis A, B, E; dengue virus) (*3*). It has been estimated that 390 million dengue virus infections occur a year, of which 96 million show clinical symptoms (of any severity of disease) (*4*). A growing number of reports describe links between climate variations and the emergence of "climate-sensitive infectious diseases", which would include all of the mosquito-borne diseases, including dengue, chikungunya and Zika virus disease (*5*), suggesting the global burden these diseases could be worsening. Dengue is endemic in more than 120 countries, with about 3.9 billion people at risk of infection (*6*). Liver injury and failure may complicate the disease course in a substantial portion of individuals affected by dengue; in an analysis of 347 patients hospitalized for dengue during one outbreak in Thailand, 219 patients (63%) had hepatic failure (*7*).

Heat stroke is another cause of acute liver failure. The global incidence of heat stroke is difficult to estimate due to lack of an accepted system to capture and report cases. In the USA, for example, one study estimated more than 4100 emergency department visits for heat stroke occur each year, an annual national incidence rate of 1.34 visits/100 000 people and a case fatality rate of 3.4% (*8*).

Amatoxin toxicity from consumption of poisonous mushrooms is a global problem, although it is difficult to estimate incidence because of the great likelihood of underreporting. While more common in some regions such as

Europe, the literature includes reports of mushroom poisoning in many regions around the world. People with mushroom poisoning who develop acute liver failure have a poor prognosis in the absence of considerable supportive care and potentially liver transplantation (*9*, *10*).

Acute liver failure caused by excess alcohol intake is another serious condition, with an estimated 30 day mortality of 30% (*11*). The exact incidence is unknown, but some estimates suggest that up to 20% of alcoholics suffer from acute liver failure (*12*). The estimated global prevalence of heavy episodic drinking was about 18% in 2016, and such drinking was more common in some areas such as Eastern Europe and sub-Saharan Africa (*13*), suggesting that some regions may be at risk of an increased prevalence of this type of acute liver failure.

Summary of evidence: benefits (from the application)

General non-paracetamol-induced acute liver failure

A 2015 systematic review and meta-analysis of four clinical trials (616 participants, 331 receiving N-acetylcysteine (oral or intravenously) and 285 controls) evaluated the efficacy and safety of N-acetylcysteine in non-paracetamol-associated acute liver failure (*14*). For the outcome of overall survival, no significant difference was identified between treatment groups (71% versus 67%; odds ratio (OR) 1.16, 95% confidence interval (CI) 0.81 to 1.67. Significant differences favouring the N-acetylcysteine group were observed for the outcomes of transplant-free survival (41% versus 30%, OR 1.61, 95% CI 1.11 to 2.34) and post-transplantation survival (85.7% versus 71.4%, OR 2.44, 95% CI 1.11 to 5.37).

A randomized study of 80 patients with non-paracetamol-induced acute liver failure evaluated the effect of N-acetylcysteine treatment on mortality, as well as efficacy and safety (*15*). More patients (72.5%) survived in the N-acetylcysteine group than in the control group (47.5%; $P = 0.025$) and among those who survived, the length of hospital stay was about 2.5 days shorter in the group treated with N-acetylcysteine ($P = 0.002$).

Heat stroke-associated acute liver failure

Three case reports have suggested improvement in liver function and other clinical outcomes associated with use of intravenous N-acetylcysteine in patients with heat-related acute liver failure (*16–18*).

Severe acute alcoholic hepatitis

A systematic review of 22 studies (2621 participants) evaluated the comparative effectiveness of five pharmacological interventions for the treatment of acute alcoholic hepatitis requiring hospitalization (*19*). A network meta-analysis found

good-quality evidence that corticosteroids alone (relative risk (RR) 0.54, 95% credible interval (CrI) 0.39 to 0.73), or in combination with N-acetylcysteine (RR 0.15, 95% CI 0.05 to 0.39) or pentoxifylline (RR 0.53, 95% CrI 0.36 to 0.78), reduce the risk of short-term mortality. Addition of N-acetylcysteine to corticosteroids may be superior to corticosteroids alone for reducing short-term mortality. No treatment was effective in reducing medium-term mortality.

Mushroom-induced acute liver failure

A systematic review of 13 studies (506 participants) evaluated the efficacy and safety of N-acetylcysteine in patients suffering amatoxin intoxication (*20*). Mortality in patients treated with N-acetylcysteine was 8% excluding liver transplant cases and 11% including liver transplant cases. The liver transplantation rate was 4.3%. Various laboratory values related to liver function and coagulopathy improved over 4–7 days after mushroom ingestion. Anaphylactic reactions occurred in 5% of cases. The review concluded that N-acetylcysteine treatment, combined with other therapies, appears to be safe and beneficial in this type of poisoning.

Acute viral hepatitis

Two small retrospective case series describe N-acetylcysteine use in children with acute liver failure in the context of acute viral hepatitis (*21*,*22*). Hepatitis A was the most common etiology. Both reports indicated improvement of liver enzymes and coagulation parameters and satisfactory medication tolerance with the use of N-acetylcysteine in this population.

Dengue

A retrospective cohort study (*23*), five case series (*24–28*), and seven case reports (*29–35*) including a total of 43 patients with dengue infection receiving N-acetylcysteine in addition to usual care were identified. Dengue-related illnesses ranged in severity, but no patients appeared to have mild disease. Outcome measures included liver function tests, mortality, measures of morbidity such as need for transplant, length of hospital stay and other laboratory measures relevant to dengue and its sequelae. All patients recovered except for three patients with disease level III–IV who already had dengue-associated acute liver failure before treatment. In one case with dengue-associated severe hepatitis (a 53-year-old), liver enzymes reached peak values of aspartate aminotransferase of 16261 U/L and alanine aminotransferases of 4545 U/L on day 4 of admission (day 7 of illness) before N-acetylcysteine treatment (*31*). After treatment, there was marked improvement in liver enzyme values, with levels dropping by more than half after 48 hours of treatment. In a retrospective case series, 13 people with moderate to severe hepatitis received N-acetylcysteine and had hepatic recovery faster than less sick patients who

did not receive N-acetylcysteine (*23*). The application also summarized data from case series and case reports that described gradual normalization of liver function tests in patients receiving N-acetylcysteine for moderate to severe dengue.

Summary of evidence: harms (from the application)

The safety and tolerability profile of N-acetylcysteine as an antidote for the treatment of paracetamol poisoning is well established. Adverse events observed in the literature presented in the application are consistent with the broader evidence on N-acetylcysteine.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the management of acute liver failure are not currently available.

Costs/cost-effectiveness

No cost–effectiveness data were presented in the application.

N-acetylcysteine is widely used globally and is generally affordable. Considering liver transplantation as an extreme outcome of acute liver failure, liver transplantation has varied costs and availability in different settings; in the USA, for example, it has been reported that the average liver transplant costs more than US$ 800 000 per patient (*36*). The resources required for transplant and follow-up are likely substantial in most settings, compounded further by the limited availability of organs for transplant. The comparatively low cost of N-acetylcysteine and the potential for averting significant adverse outcomes later, such as the need for liver transplantation, would suggest it is a cost-effective treatment.

Availability

N-acetylcysteine is widely available across the world. To date, N-acetylcysteine does not have regulatory approval for the prevention or treatment of liver injury from causes other than paracetamol overdose.

Other considerations

The applicants reviewed a set of data from a phenome-wide association study (PheWAS). These studies can identify diseases or conditions (phenotypes) that are associated with a specific gene/genetic variant (*37*). PheWAS makes use of existing data from the Exomechip genotyping platform (about 250 000 coding

variants across the protein coding region of the genome) and electronic health records of about 35 000 patients. Because PheWAS rationale can be applied to identify other types of phenotypic manifestations of pharmacological targeting (such as with N-acetylcysteine) of a given gene product in humans, these methods are used for drug repurposing (*38*). As a glutathione synthetase "stimulator", N-acetylcysteine is hepatoprotective. This is has been established in its use in paracetamol overdose. The phenotypes associated with a missense single nucleotide polymorphism (R418Q) in the glutathione synthetase gene are risk-causing, so in this regard we can say the single nucleotide polymorphism is behaving as a glutathione synthetase inhibitor (the opposite of the drug). Thus, a variety of liver phenotypes strengthens the inference that decreased glutathione synthetase is associated with a broad range of liver injury, as is true in the etiologies of acute liver failure represented in the current application.

Committee recommendations

The Expert Committee noted acute liver failure is relatively rare, but has a range of etiologies, including medicine-associated toxicity, viral infections and other causes. In some cases, liver transplant is needed and the prognosis can be poor with high short-term mortality, particularly where transplantation is unavailable.

N-acetylcysteine is currently included in the Model lists for use as an antidote to paracetamol overdose. The Committee noted this application is for expanding the indication of N-acetylcysteine to conditions where acute liver failure is mediated by glutathione deficiency, including dengue and other causes of viral hepatitis, mushroom toxicity, alcoholic hepatitis and heat stroke. These conditions affect numerous people, especially in low- and middle-income countries.

From the review of the literature presented, the Committee considered that the effects of N-acetylcysteine on mortality, need for transplant and duration of hospitalization are still not established because of the very low certainty of the available evidence. The Committee noted the heterogeneous effects across different patient populations, and the limited information on patient age or severity of illness due to insufficient trial data. The Committee also noted the lack of clinical guidelines on the use of N-acetylcysteine for indications other than paracetamol-induced liver toxicity. In addition, the Committee noted that N-acetylcysteine does not have regulatory approval for indications other than paracetamol overdose.

The Expert Committee therefore did not recommend listing N-acetylcysteine for the new indication of non-paracetamol-induced acute liver failure because of limited confidence in the estimates of benefits. The Committee considered that higher quality studies may be feasible and would be beneficial to inform any future consideration for listing N-acetylcysteine.

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Section 5: ANTICONVULSANTS/ANTIEPILEPTICS

Valproic acid (sodium valproate) – change to listing – EML and EMLc

Valproic acid (sodium valproate) **ATC Code: N03AG01**

Proposal

Transfer of the current listings of valproic acid (sodium valproate) on the EML and EMLc from the core to the complementary list, and addition of a cautionary note about its use with pregnant women and women and girls of child-bearing potential.

Applicant

Independent Fetal Anticonvulsant Trust (INFACT), United Kingdom of Great Britain and Northern Ireland

WHO Technical Department

Mental Health and Substance Use

EML/EMLc

EML and EMLc

Section

5. Anticonvulsants/antiepileptics
24.2.2 Medicines used in bipolar disorders

Dose form(s) & strength(s)

All currently listed dose forms and strengths

Core/Complementary

Transfer from core to complementary list

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Valproic acid has been included on the EML as a medicine for epilepsy since 1979. It was included on the first EMLc for this indication in 2007.

Since 1997, valproic acid has also been included on the EML for the treatment of bipolar disorder in adults.

Public health relevance (burden of disease)

Valproic acid is used in the treatment of labelled indications of epilepsy and bipolar disorder, as well as off-label indications such as migraine prophylaxis, neuropathic pain and behavioural disturbances in dementia.

Valproic acid is a known human teratogen, and its use during pregnancy is associated with an increased risk of birth defects and neurodevelopmental disorders in children exposed to the drug in utero (*1–7*). To address these risks, regulatory agencies in many parts of the world, including Europe, the United Kingdom and the USA have issued guidance and/or restrictions on the use of valproic acid in pregnancy and in women and girls of child-bearing potential (*8–11*).

Summary of evidence: benefits (from the application)

Not applicable.

Summary of evidence: harms (from the application)

The application reproduced the warnings, precautions and contraindications for the use of valproic acid in female children, adolescents and women of child-bearing potential and in pregnancy from past and current summaries of product characteristics.

The application also briefly described two studies that evaluated the effects of antiepileptic medicines, including valproic acid, on cognitive and neurodevelopmental outcomes in children exposed to the drugs in utero.

The NEAD study was a prospective, observational multicentre study conducted in the United Kingdom and USA that evaluated the effects of commonly prescribed antiepileptic medicines (carbamazepine, lamotrigine, phenytoin or valproic acid) on cognitive outcomes in children up to 6 years of age born to mothers receiving these medicines during pregnancy (*12*). The primary outcome of the study was intelligence quotient (IQ) of children at age 6. A total of 244 children were included in the age 6 analysis. The study found that the age 6 IQ was lower in children exposed to valproic acid compared with children exposed to other antiepileptic drugs. Children exposed to valproate also did poorly on measures of verbal and memory abilities compared with children exposed to other antiepileptic drugs. These effects of valproic acid were dose-dependent.

Another prospective, observational study of children born to women with epilepsy compared with a control group of children born to women without epilepsy was conducted in the United Kingdom (*1*). This study reported an increased risk of neurodevelopmental disorders in children exposed to valproic acid as monotherapy (adjusted odds ratio (aOR) 6.05, 95%CI 1.65 to 24.53) and as polytherapy (aOR 9.97, 95% CI 1.82 to 49.40) compared with controls. Autistic spectrum disorder was the most frequent diagnosis. No significant

increase in neurodevelopmental disorders was found among children exposed to carbamazepine or lamotrigine as monotherapy.

Additional evidence (not in the application)

Not applicable

WHO guidelines

The WHO *mhGAP intervention guide*, version 2.0 for mental, neurological and substance use disorders in non-specialized health settings (*13*) includes recommendations for the use of valproic acid in the treatment of epilepsy and manic episodes in bipolar disorder. The guide also includes warnings to avoid the use of valproic acid in women of child-bearing age and during pregnancy and breastfeeding due to the known risks to the child.

The *WHO Pharmaceuticals Newsletter* (*14*) states the following in relation to the use of valproic acid in pregnancy or in females of child-bearing potential.

"*Medicines containing valproate (e.g. sodium valproate, valproic acid, divalproex) should be avoided in pregnant women or in females of child-bearing potential, unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects (such as spina bifida, facial, skull, limb and heart malformations) and developmental disorders in infants who are exposed to valproate in the womb. When alternative treatments are not available or appropriate, female patients prescribed valproate medicines should be made aware of the risk and use effective contraception methods.*"

Costs/cost-effectiveness

Not applicable

Availability

Not applicable

Other considerations

Not applicable

Committee recommendations

The Expert Committee recognized the serious risks associated with the use of valproic acid in pregnant women and in females of child-bearing potential. While most of the evidence and regulatory measures described in the application are from Europe, the risks with valproate when prescribed to women and girls of child-bearing potential are equally relevant globally.

Sodium valproate is currently listed as an essential medicine for use in the treatment of epilepsy and bipolar disorder, indications for which it has

regulatory approval. Furthermore, valproic acid is recommended for the management of epilepsy and bipolar disorder in the WHO *mhGAP intervention guide*. These guidelines also include a strong recommendation to avoid the use of valproic acid in women of child-bearing age. The Committee considered that inclusion of a cautionary note with the listings of valproic acid to indicate that use should be avoided in pregnant women and females of child-bearing potential was appropriate, although it is aware the EML does not replace prescribing information issued by national medicine regulatory authorities.

The Committee did not recommend transferring the listing of valproic acid from the core to the complementary list. The Committee considered doing so may have negative implications for access to valproic acid and undermine its important role in the management of epilepsy and bipolar disorder, particularly in resource-constrained settings, where access to valproate and alternative treatments is limited.

The Committee supported the need for patient and prescriber education on the risks and appropriate use of valproic acid, including its use for off-label indications, but considered this to be a responsibility of the relevant national decision-makers.

The Committee recommended the following note be included with the listings for valproic acid on the EML and EMLc:

"Avoid use in pregnancy and in women and girls of child-bearing potential unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb."

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Section 6: ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.4 Medicines for taeniid cestode cysts (new-subsection)

Albendazole, mebendazole, praziquantel – new indication – EML and EMLc

Albendazole	**ATC Code: P02CA03**
Mebendazole	**ATC Code: P02CA01**
Praziquantel	**ATC Code: P02BA01**

Proposal

Extension of the indications for albendazole, mebendazole and praziquantel on the EML and EMLc to include treatment for diseases caused by taeniid cestode cysts: cystic echinococcosis, alveolar echinococcosis and neurocysticercosis.

Applicant

WHO Department of the Control of Neglected Tropical Diseases

WHO technical department

Control of Neglected Tropical Diseases

EML/EMLc

EML and EMLc

Section

6.1.4 Cysticidal medicines (new subsection)

Dose form(s) & strength(s)

Albendazole: Tablet (chewable): 400 mg
Mebendazole: Tablet (chewable): 500 mg
Praziquantel: Tablet: 500 mg, 600 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Albendazole, mebendazole and praziquantel have not been previously considered for inclusion on the Model Lists for treatment of diseases caused by taeniid cestode cysts.

All three medicines are included on the Model Lists for other anthelminthic indications.

Public health relevance (burden of disease)

Cystic echinococcosis

Human infection with Echinococcus granulosus leads to the development of one or more cysts located most often in the liver and lungs, and less frequently in the bones, kidneys, spleen, muscles and central nervous system. The asymptomatic incubation period of the disease can last many years until hydatid cysts grow large enough to trigger clinical signs. The clinical signs of E. granulosus infection vary depending on the number, location and size of the cysts. They and manifest commonly as pain and compromised organ function, which worsen as the cysts enlarge. Infection is debilitating and fatal in some patients. Cystic echinococcosis is globally distributed and is most prevalent in communities where pastoral activities predominate, as the most common transmission cycle involves dogs and sheep (but can also involve other livestock species). Such communities are found in all countries bordering the Mediterranean Sea, many regions and countries in central Asia, and parts of China, Australia and South America. In endemic regions, the incidence of cystic echinococcosis in humans can reach more than 50 per 100 000 person-years, and prevalence levels as high as 5–10% may occur in parts of Argentina, Central Asia, China, East Africa and Peru (*1*).

Alveolar echinococcosis

Infection in humans with *E. multilocularis* is characterized by an asymptomatic incubation period of 5–15 years and the slow development of a primary tumour-like lesion, which is usually located in the liver. Clinical signs include weight loss, abdominal pain, general malaise and signs of liver failure. Larval metastases may spread either to organs adjacent to the liver (for example, the spleen) or to distant locations (such as the lungs or the brain) by dissemination of the parasite via the blood and lymphatic system. If left untreated, alveolar echinococcosis is progressive and universally fatal. Alveolar echinococcosis is confined to the northern hemisphere, in particular to regions of China, the Russian Federation, Central Asia and countries in continental Europe.

Neurocysticercosis

Neurocysticercosis is caused by the larval stages of *Taenia solium* encysting in the central nervous system. In many cases, neurocysticercosis is asymptomatic,

but the most common sign of symptomatic neurocysticercosis are epileptic seizures. Neurocysticercosis is thought to be the leading cause of preventable epilepsy worldwide. Neurocysticercosis can also cause chronic headaches, blindness, focal deficits and psychiatric symptoms. Clinical signs will vary depending on the number, location and size of the cysts. Parenchymal brain cysts are associated with seizures and epilepsy and are more amenable to treatment, particularly in individuals with viable or degenerating cysts. Extraparenchymal neurocysticercosis is associated with hydrocephalus, meningitis, focal neurological deficits, and sometimes death, and it is more difficult to treat. *T. solium* is endemic in South and Central America, South and South-East Asia, and parts of sub-Saharan Africa where pigs roam free (pigs are the intermediate host), and where open defecation is practised. It is a disease of poverty, principally affecting the most marginalized communities. Few data are available on the burden of disease caused by *T. solium*. Two different research groups estimated the number of epilepsy cases associated with neurocysticercosis globally to be 370 710 in 2010 (*2*) and 1.93 million in 2015 (*3*). WHO estimates the burden of *T. solium* to be 2 788 426 disability-adjusted life years (*2*). In areas endemic for cysticercosis, about 30% of people with epilepsy show lesions of neurocysticercosis on imaging (*4*).

Summary of evidence: benefits (from the application)

Cystic echinococcosis and alveolar echinococcosis

Benzimidazoles (albendazole and mebendazole) are indicated for patients with inoperable liver or lung cystic echinococcosis (patients with multiple cysts in two or more organs, or with peritoneal cysts). Small (< 5 cm) cystic echinococcosis 1 and cystic echinococcosis 3a cysts in the liver and lung respond well to benzimidazole alone. Benzimidazoles should be used to prevent recurrence following surgery, or puncture, aspiration, injection, reaspiration (PAIR) (*5*).

Albendazole is currently the drug of choice for cystic echinococcosis. Mebendazole may be used if albendazole is not available or not well tolerated. The standard dosage of albendazole of 10–15 mg/kg a day for 3–6 months has about a 30% cure rate. The number of patients with clinical or ultrasound improvement increases with longer durations of treatment while the proportion of patients with cure does not significantly change (*6*, *7*). Albendazole is more effective in young patients and for small cystic echinococcosis 1 and cystic echinococcosis 3a cysts. Benzimidazoles are less effective for cystic echinococcosis 2 and cystic echinococcosis 3b (*6*, *7*). The importance of cyst stage and size in determining response to treatment was confirmed by a systematic review (*8*). Sole treatment with a benzimidazole is also indicated for patients with inoperable liver or lung

cystic echinococcosis; patients with multiple cysts in two or more organs and patients with peritoneal cysts. Drugs alone are not effective against giant cysts (> 10 cm in diameter) (*9*).

Benzimidazoles are also used as an adjunct to surgery or interventional procedures to: reduce the cyst's internal tension; complement mechanical removal of the cyst or the chemical sterilization of the parasite; and prevent secondary echinococcosis (*9*). Albendazole in combination with PAIR has been shown to reduce the chance of cyst recurrence (*10*).

Benzimidazole treatment is required for several years in all patient with inoperable alveolar echinococcosis and following surgical resection of the parasite lesions. Since residual parasite tissue may remain undetected at radical surgery, including liver transplantation, benzimidazole should be given for at least 2 years and these patients should be monitored for a minimum of 10 years for possible recurrence. Presurgical benzimidazoles administration is not recommended except in the case of liver transplantation. Albendazole is the drug of choice for alveolar echinococcosis. Mebendazole may be given if albendazole is not available or not tolerated.

Controlled, but non-randomized, studies showed that long-term benzimidazole treatment improved the 10-year survival rate in patients with alveolar echinococcosis who had not had radical surgery compared with historical untreated control patients, from 6–25% to 80–83%, respectively (*11*), and prevented recurrences after radical surgery (*12*).

Neurocysticercosis

A meta-analysis of 11 randomized trials of albendazole and praziquantel for the treatment of neurocysticercosis evaluated the effect of cysticidal drugs on neuroimaging and clinical outcomes in 942 patients with neurocysticercosis (464 with cystic lesions, 478 with enhancing lesions) (*13*). Cysticidal drug therapy was associated with significantly higher rate of complete resolution of cystic lesions (44% versus 19%; $P = 0.025$) and with improved, though not statistically significant, resolution for enhancing lesions (72% versus 63%; $P = 0.38$). Excluding an outlier trial from the analysis, the difference in response for enhancing lesions became statistically significant (69% versus 55%; $P = 0.006$). The risk of seizure recurrence was lower after cysticidal treatment in patients with enhancing lesions (14% versus 37%; $P = 0.001$). The single trial evaluating the frequency of seizures in patients with cystic lesions showed a 67% reduction in the rate of generalized seizures with treatment ($P = 0.006$).

Summary of evidence: harms (from the application)

Albendazole, mebendazole and praziquantel have been used as treatments of choice for diseases caused by taeniid cestodes cysts for over 30 years.

Cystic echinococcosis and alveolar echinococcosis

Benzimidazoles are well tolerated in 70–80% of cases, but more adverse effects are seen in patients with immunosuppression (*14*). The most commonly reported side-effects are hepatotoxicity, elevation of aminotransferases, proteinuria, transient hair loss, gastrointestinal disturbances, leukopenia, thrombocytopenia and neurological symptoms, including sleeplessness and vertigo (*15*).

In cystic echinococcosis, benzimidazoles are contraindicated in cysts at risk of rupture and in early pregnancy. In addition, benzimidazoles must be used with caution in patients with chronic liver disease and avoided in patients with bone-marrow depression. In alveolar echinococcosis, due to the severity of the condition, contraindications are limited mainly to life-threatening side-effects (*5*).

For cystic echinococcosis, follow-up visits, including ultrasound examination should be performed every 3–6 months initially, and then annually once the situation is stable. Leukocyte counts and aminotransferase measurements are recommended at monthly intervals to monitor for adverse reactions (*5*). For alveolar echinococcosis, monitoring of liver enzymes and blood cell counts are recommended every 2 weeks for the first 3 months, then monthly for 1 year, then every 3 months. Decreased leukocyte count below 1 x 10^9/L indicates benzimidazole toxicity and warrants treatment withdrawal (*5*).

Neurocysticercosis

The main side-effects of albendazole in patients treated with doses of 15 mg/kg a day or lower for 28 days are due to parasiticidal activity and treatment-induced inflammation and include headaches, seizures and dizziness. There is a transient increase in the number of seizures after therapy. Hepatotoxicity and leukopenia are known adverse effects of albendazole and are considered relative contraindications to continued use. Monitoring of liver enzymes and complete blood counts is recommended during the first month of treatment (*16*).

Randomized trials of albendazole for neurocysticercosis have found no significant differences in adverse events between patients treated with albendazole or placebo (*17*, *18*).

The main side-effects of praziquantel in patients with neurocysticercosis are due to its cysticidal activity, and include headache, dizziness and seizures. Doses up to 100 mg/kg a day for up to 28 days have been used in neurocysticercosis without additional laboratory adverse effects. More than 10% of patients treated with praziquantel experience gastrointestinal side-effects including nausea, vomiting and abdominal pain. As with albendazole therapy, monitoring of liver enzymes and complete blood counts is recommended (*16*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the management of *T. solium* neurocysticercosis were approved (with revisions) by the WHO Guidelines Review Committee in October 2020.

The guideline includes two proposed recommendations on antiparasitic treatment.

Recommendation 1: Anthelminthic therapy in combination with corticosteroids should be provided to individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts for better outcomes in terms of cyst resolution, and potentially improved seizure control (strong recommendation, moderate quality of evidence).

Rationale: The quality of evidence was moderate for the effect of anthelminthic therapy on cyst resolution, and for the effect of anthelminthic therapy in improving seizure control. It was decided that this should be a strong recommendation because the potential benefit – cyst resolution and possibly improved seizure control – likely outweighs any potential harm associated with the use of anthelminthic therapy.

Remarks:

- Albendazole, in combination with corticosteroids, has been shown to be superior to either corticosteroids only or no treatment at all.
- Dual therapy with praziquantel and albendazole has been shown to be more effective than treatment with albendazole alone in individuals with two or more parenchymal brain cysts.
- Evidence on the use of albendazole in pregnant women was not evaluated; pregnant women should seek expert advice before receiving treatment with albendazole.
- There is no evidence that anthelminthic therapy in children should be different to that of adults.
- Although evidence is lacking, the clinical experience of experts indicates that anthelminthic drugs should not be used in patients with symptomatic neurocysticercosis and encephalitis. If inflammation is pronounced in these cases, patients should be treated with corticosteroids alone.

- Enhanced dosing schedules of corticosteroids (i.e. of 28 days duration) were associated with better clinical outcomes compared with shorter dosing schedules (e.g. of 10 days duration); however, this may not be the optimal schedule.

Recommendation 2: Anthelminthic therapy in combination with corticosteroids should be provided to individuals with symptomatic neurocysticercosis and a single enhancing lesion for better outcomes in terms of cyst resolution and potentially improved seizure control (moderate recommendation, moderate to very low quality of evidence).

Rationale: The quality of evidence was considered low for the effect of anthelminthic therapy on cyst resolution, and very low for the effect of anthelminthic therapy in improving seizure control. It was decided that this should be a conditional recommendation because of the methodological differences between studies. However, all studies found the combination of albendazole and corticosteroids to have a beneficial effect.

Remarks:

- Many studies are available on the use of anthelminthic therapy in combination with corticosteroids in individuals with a single enhancing lesion; however, significant limitations are present in the synthesis of these data in existing meta-analyses.

The application included a summarized version of the evidence on which these recommendations were based. Notably, only studies related to albendazole were included, because the studies that included praziquantel had methodological problems (*19–21*). However, based on expert opinion, and a study of the combination of albendazole and praziquantel (*22*), praziquantel was also included in the recommendation.

Costs/cost–effectiveness

The cost of albendazole (400 mg tablets) varies widely. The cost of 3 months of treatment for cystic echinococcosis in endemic countries for generic or locally produced albendazole ranges from US$ 39.60 in Turkey to US$ 987.30 in Chile.

For the minimum 14-day treatment of neurocysticercosis in endemic countries, the cost for generic or locally produced albendazole ranges from US$ 10.50 in Zambia to US$ 39.50 in Uganda. For praziquantel, the 14-day treatment costs range from US$ 16.80 in Uganda to US$ 132.30 in Mexico.

Mebendazole tablets are donated to WHO from the manufacturer.

Availability

Albendazole 400 mg tablets are available in originator and generic brands.

Mebendazole 500 mg tablets are available in originator and generic brands. WHO receives donation of 500 mg mebendazole tablets from Johnson & Johnson.

Praziquantel 500 mg and 600 mg tablets are produced by Merck. Praziquantel 600 mg tablets are also produced by Bayer, and donated to WHO for the treatment of *T. solium* taeniasis.

Other considerations

Comments on the application were received from Médecins Sans Frontières, in which strong support for the proposed listings was expressed.

Committee recommendations

The Expert Committee acknowledged that diseases caused by taeniid cestode cysts (cystic echinococcosis, alveolar echinococcosis and neurocysticercosis) are neglected tropical diseases with a global disease burden for which a public health need exists for effective treatment.

The Committee noted that benzimidazoles are established as the treatment of choice for cystic echinococcosis and alveolar echinococcosis; anthelminthic therapy with albendazole or praziquantel is the treatment of choice for neurocysticercosis. These recommendations are supported by evidence for benefit from non-randomized and randomized clinical trials, expert consensus and in WHO and other international treatment guidelines. The Committee also noted that albendazole, mebendazole and praziquantel have been included on the Model Lists as anthelminthic treatments for other indications for more than 30 years, and their use in clinical practice is well established.

The Committee therefore recommended expanding the listings of albendazole, mebendazole and praziquantel on the EML and EMLc to include new indications for the diseases caused by taeniid cestode cysts. Specifically, albendazole and mebendazole for treatment of cystic echinococcosis and alveolar echinococcosis, and albendazole and praziquantel for treatment of neurocysticercosis. Noting the need for specialized diagnostic, monitoring and medical care for patients with these diseases, listing was recommended on the Complementary list, in a new sub-section for cysticidal medicines.

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6.2 Antibacterials

6.2.1 Access group antibiotics

6.2.2 Watch group antibiotics

6.2.3 Reserve group antibiotics

Antibiotics for bronchitis and bronchiolitis – new indication – EML and EMLc

Bronchitis and bronchiolitis

Applicant

Mark Loeb, Dominik Mertz, Paul Alexander; McMaster University, Hamilton, Canada

Introduction

Acute bronchitis is a very common respiratory syndrome that frequently leads to the prescription of antibiotics, particularly during peak periods of respiratory virus circulation such as in the autumn and winter, thus contributing to the emergence and spread of antimicrobial resistance. There are no recent estimates of the global burden of acute bronchitis, but it is one of the most common reasons for medical visits in many countries. Although infection is thought to trigger episodes of acute bronchitis, pathogens are often not identified and respiratory viruses are responsible for most episodes. Bronchitis is characterized by a transient inflammation of the trachea and major bronchi and is diagnosed clinically based on the new onset of a cough. The clinical presentation may also include sputum production, dyspnoea and wheeze.

Bronchiolitis is inflammation of the bronchioles that occurs in young children and infants for which the cause is viral, predominantly respiratory syncytial virus (RSV). Symptoms include cough, fever, wheezing and difficulty breathing. A recent study estimated that about 33.1 million episodes of acute lower-respiratory tract infections caused by RSV in children younger than 5 years occurred globally in 2015, resulting in 3.2 million hospital admissions and about 60 000 in-hospital deaths. (*1*).

Summary of evidence (from the application)

The application presented the results of a search for systematic reviews and meta-analyses of antibiotic therapy for bronchitis and bronchiolitis.

Acute bronchitis

Two systematic reviews of antibiotic therapy for acute bronchitis were identified and reviewed in detail (*2*, *3*).

A 2017 Cochrane systematic review of 17 randomized controlled trials (5009 participants) evaluated the effects of antibiotic therapy compared

with placebo or no treatment for acute bronchitis (*2*). Antibiotics included amoxicillin, amoxicillin–clavulanic acid, azithromycin, cefuroxime, doxycycline, erythromycin and trimethoprim–sulfamethoxazole. No difference in clinical improvements was seen between antibiotic and placebo groups (11 studies, 3841 participants; risk ratio (RR) 1.07, 95% confidence interval (CI) 0.99 to 1.15). Participants given antibiotics were less likely to have a cough (four studies, 275 participants, RR 0.64, 95% CI 0.49 to 0.85) and night cough (four studies, 538 participants, RR 0.67, 95% CI 0.54 to 0.83) at follow-up, however there was no difference in productive cough. A shorter cough duration (seven studies, 2776 participants) was observed with antibiotics (mean difference –0.46 days, 95% CI –0.87 to –0.04 days). There was a significant increase in adverse events in the antibiotic group (12 studies, 3496 participants, RR 1.20, 95% CI 1.05 to 1.36).

A systematic review of nine randomized controlled trials (774 participants of whom more than 276 were smokers) evaluated the efficacy of antibiotic therapy compared with placebo for smokers with acute bronchitis (*3*). Antibiotics included doxycycline, erythromycin and trimethoprim–sulfamethoxazole and doxycycline. A meta-analysis was not done because of the lack of subgroup reporting for smokers. Antibiotics showed no overall benefit in five of the nine trials, while adverse events occurred on average in 11% of participants in the placebo group and 16% in the antibiotic group.

Bronchiolitis

Two systematic reviews of antibiotic therapy for bronchiolitis were identified, one for acute bronchiolitis (*4*) and the other for persistent cough and wheezing following acute bronchiolitis (*5*).

A 2014 Cochrane systematic review of seven randomized controlled trials (824 participants) evaluated antibiotics for bronchiolitis in children younger than 2 years (*4*). Heterogeneity of the trials precluded a meta-analysis for some outcomes. No deaths were reported among the groups included in the seven trials. Pooling of three trials showed no difference between antibiotics (azithromycin) and placebo (mean difference in days of supplemental oxygenation –0.20, 95% CI–0.72 to 0.33). The three trials (350 participants overall) were small and the point estimates were all compatible with a reduction in symptoms of less than 1 day. Another three studies showed no difference between antibiotic (azithromycin) and placebo groups for length of hospital stay (mean difference in days –0.58, 95% CI –1.18 to 0.02); similarly, point estimates were < 1 day. Two of the trials found no difference in symptom measures with antibiotics (intravenous ampicillin, oral erythromycin) versus control, with point estimates indicating more symptoms in those treated with antibiotics in one trial.

A 2017 Cochrane systematic review of two randomized controlled trials (249 participants) evaluated antibiotic treatment for persistent cough or wheeze following acute bronchiolitis in children (*5*). No significant differences were

found between the antibiotic (azithromycin and clarithromycin) and placebo groups in the proportion of children with persistent symptoms at follow-up (odds ratio (OR) 0.69, 95% CI 0.37 to 1.28), rehospitalization at 6 months (OR 0.54, 95% CI 0.05 to 6.21) and wheezing at 6 months (OR 0.47, 95% CI 0.06 to 3.95).

Guidelines (from the application)

The application presented the results of a search for clinical practice guidelines (CPGs) for the use of antibiotics for acute bronchitis and bronchiolitis.

Acute bronchitis

Two clinical practice guidelines were identified (*6*,*7*). The 2019 NICE (United Kingdom) guideline recommends not routinely offering an antibiotic to treat an acute cough associated with acute bronchitis in patients who are not systemically unwell or at high risk for complications (*6*). The guidelines suggest offering an immediate antibiotic if the patient is systemically very unwell at face-to-face examination. The guideline refers to the NICE guideline on pneumonia to consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia (rather than bronchitis alone) has not been made and it is not clear whether antibiotics should be prescribed (*8*). If an antibiotic is to be prescribed, the NICE guidelines recommend doxycycline as the first-choice antibiotic with amoxicillin and clarithromycin being alternative choices. For children and young adults, amoxicillin is recommended as the first choice.

The 2016 practice guidelines for acute respiratory tract infection in adults by the American College of Physicians and Centers for Disease Control and Prevention do not recommend antibiotics for patients with acute bronchitis *(7)*.

Bronchiolitis

Three clinical practice guidelines for bronchiolitis were identified. The American Academy of Pediatrics guideline recommends that antibiotics should not be used unless there is a concomitant bacterial infection or a strong suspicion of one (*9*). The guidelines outline that the incidence of serious bacterial infection in children with bronchiolitis is low.

The Italian Inter-Society consensus guideline for treatment and prevention of bronchiolitis in newborns and infants also specifies that antibiotics are not to be used routinely because of the risk of side-effects, the high costs and the risk of antibiotic resistance (*10*). The Canadian Pediatric Society guidelines specify that bacterial infection in otherwise healthy children with bronchiolitis is extremely rare, research on the effect of antibiotics is limited and that antibiotic treatment has failed to show benefit for this condition (*11*). The guideline recommends that antibiotics should not be used except in cases in which there is clear evidence or strong suspicion of a secondary bacterial infection.

Rationale for antibiotic selection (from the application)

Acute bronchitis

Based on the evidence from randomized controlled trials and the clinical practice guidelines, antibiotic treatment is not recommended for acute bronchitis in otherwise healthy people.

Bronchiolitis

Based on the evidence from randomized controlled trials and the clinical practice guidelines, antibiotic treatment is not recommended for bronchiolitis in otherwise healthy children unless there is clear evidence of or a strong suspicion of a secondary bacterial infection.

Committee considerations (e.g. additional evidence, dose/duration, costs)

The WHO *Pocket book of hospital care for children* recommends antibiotic treatment in children with bronchiolitis only when pneumonia is suspected (*12*):

- If the infant is treated at home, give amoxicillin (40 mg/kg twice a day) orally for 5 days only if the child has signs of pneumonia (fast breathing and lower chest wall indrawing).
- If there are signs of severe pneumonia, give ampicillin (50 mg/kg) or benzylpenicillin (50 000 U/kg) intramuscularly or intravenously every 6 hours for at least 5 days, and gentamicin 7.5 mg/kg intramuscularly or intravenously once a day for at least 5 days.

These antibiotics are already included on the EMLc as treatment options for children with community-acquired pneumonia.

EML listings

No additional listings for antibiotics for the treatment of acute bronchitis or bronchiolitis are proposed.

Committee recommendations

The Expert Committee noted that bronchitis and bronchiolitis are frequent causes of antibiotic use around the world, even though most cases are caused by respiratory viruses and not bacteria. The Committee acknowledged that inappropriate or unnecessary use of antibiotics for bronchitis and bronchiolitis can contribute to the development of antimicrobial resistance and should be discouraged.

The Committee noted the evidence presented from systematic reviews and meta-analyses indicates that antibiotics do not result in improvement in clinical outcomes in acute bronchitis and bronchitis compared with no

treatment or placebo for both conditions. The Committee further noted that international guidelines do not recommend antibiotics for treatment of patients with these conditions, unless there is clear evidence or strong suspicion of a secondary bacterial infection.

The Committee considered that the appropriate treatment for most cases of bronchitis and bronchiolitis is symptom relief and no antibiotic therapy. Therefore, the Committee did not recommend listing any antibiotics on the EML and EMLc for the treatment of bronchitis and bronchiolitis due to a lack of evidence of a meaningful clinical benefit.

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Antibiotics for ocular infections – new indications – EML and EMLc

Antibiotics for ocular infections

Applicant

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Introduction

Conjunctivitis is an inflammation or infection of the conjunctiva characterized by dilatation of the conjunctival vessels and typically with associated discharge. Most episodes are from viral infection, with bacteria being the second most common cause. In children, however, bacterial infections can be more common than viral infections. The most common bacterial pathogens causing bacterial conjunctivitis are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. *M. catarrhalis* is a frequent bacterial cause of conjunctivitis in children.

Infectious keratitis is an infection of the cornea and an important cause of visual impairment and blindness. It predominantly affects people in developing countries as well as contact lens users in developed countries. The mainstay of diagnosis is a Gram staining and culture of corneal samples to guide targeted treatment. The most common pathogens are: *Pseudomonas* sp., *Staphylococcus* sp., *Streptococcus* sp. and other Gram-negative organisms. Endophthalmitis can be exogenous (postoperative, trauma) or endogenous. Cataract surgery is the most common source of exogenous endophthalmitis with the most common causative pathogens being Gram-positive bacteria (*Staphylococcus* sp. or three *Streptococcus* sp.) while Gram-negative bacteria are a less common cause.

Endogenous endophthalmitis is caused by bacterial pathogens in about half of the cases, mostly by Gram-positive bacteria (*Staphylococcus* sp. or *Streptococcus* sp.). In East Asia, *Klebsiella pneumoniae* is reported to be the leading pathogen responsible for endogenous endophthalmitis. Microbiological diagnosis through tap biopsy or vitrectomy is required to guide targeted antibiotic treatment. Surgical debridement and/or pars plana vitrectomy is in general required if the infection spreads beyond the choroid into the vitreous. Antibiotics can be administered by topical, subconjunctival, intravitreal, and/or systemic routes.

Summary of evidence (from the application)

The application presented the results of a search for systematic reviews and meta-analyses of antibiotic therapy for ocular infections.

Conjunctivitis

Four systematic reviews were identified, including two on antibiotics for bacterial conjunctivitis (*1*, *2*) and two specific to the management of *Chlamydia trachomatis* conjunctivitis (trachoma) (*3*, *4*).

A Cochrane systematic review summarized eleven randomized controlled trials (2116 patients) that compared topical antibiotics to placebo for acute bacterial conjunctivitis (*1*). The topical antibiotics used included azithromycin, bacitracin, besifloxacin, ciprofloxacin, chloramphenicol, fusidic acid, moxifloxacin, norfloxacin and polymyxin. The authors reported a modest benefit from topical antibiotics (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.15 to 1.61) for early clinical resolution (day 2–5), and similarly for late resolution (RR 1.21, 95% CI 1.10 to 1.33) (day 6–10). There were no serious outcomes in either study arm.

An individual patient-data meta-analysis of three randomized controlled trials (626 patients) also compared topical antibiotics with placebo for acute infective conjunctivitis (*2*). Antibiotics included chloramphenicol and fusidic acid. Cure was more likely at day 7 with antibiotic treatment (risk difference 0.08, 95% CI 0.01 to 0.04), and for those with purulent discharge and mild severity of eye redness in subgroup analysis. The effect was, however, modest and, given that the infection is largely self-limiting, the authors recommended the use of topical antibiotics only in selected patients.

Neither of these two systematic reviews identified studies of head-to-head comparison of different antibiotics; therefore no systematic review data are available to guide the choice of antibiotics.

A Cochrane systematic review of antibiotic treatment for trachoma included nine studies (1961 patients) comparing topical antibiotics with placebo, eight studies (1583 patients) comparing oral and topical antibiotics, and four cluster-randomized studies comparing oral azithromycin with delayed or no treatment (*3*). There was a benefit from antibiotics versus no treatment (RR 0.78, 95% CI 0.69 to 0.89) for cure after 3 months, but no statistically significant benefit after 12 months of follow-up (RR 0.74, 95% CI 0.55 to 1.0). No interaction effect was seen between studies comparing either topical or systemic antibiotics with placebo, nor was there a benefit from systemic versus topical antibiotics in studies comparing the two modes of application at 3 months (RR 0.97, 95% CI 0.81 to 1.16). However, a comparison between systemic azithromycin and topical tetracycline favoured azithromycin (RR 0.76, 95% CI 0.59 to 0.99) for the 12-month outcome of active trachoma, while there was no difference at 3 months (no effect size was reported).

A systematic review and meta-analysis of three randomized controlled trials and nine observational studies (292 patients) evaluated antibiotic treatment in neonates with chlamydial conjunctivitis (*4*). The authors assessed the efficacy of various doses of systemic macrolides. Only cure rates of each study were

reported with no direct comparisons. The only regimen that appeared to result in a lower cure rate compared to the other regimens reported was a single-dose treatment of azithromycin (60% cure rate), while a 3-day course of azithromycin and any of the regimens using 10–14 days of erythromycin had similar cure rates. No firm conclusions could be drawn on which antibiotic or regimen would be the most appropriate to use. A short course of azithromycin may be beneficial because of less concern about adherence when compared with a 14-day course of erythromycin. The cure rate of 60% in the study that used a single dose of azithromycin should be considered in the context of the original study which was a small observational study in only five neonates.

Keratitis

Two systematic reviews on antibiotic treatment for bacterial keratitis were identified (*5*, *6*).

One review included eight randomized controlled trials and five observational studies that compared topical fluoroquinolones (ciprofloxacin, lemofloxacin, levofloxacin, moxifloxacin and ofloxacin) with a combination of an aminoglycoside (amikacin, gentamicin or tobramycin) plus cephalosporin (cefazolin, cefalotin, cefamandole, cefuroxime or cephaloridine) for treatment of (suspected) bacterial keratitis (*5*). No difference was found in achieving the primary outcome of healing between the treatment groups in the randomized controlled trials (odds ratio (OR) 1.05, 95% CI 0.64 to 1.73) but a benefit for fluoroquinolones was seen in observational studies (OR 2.37, 95% CI 1.08 to 5.21). When combining the study designs, no statistically significant effect was found (OR 1.47, 95% CI 0.90 to 2.41). When limited to microbiologically confirmed bacterial keratitis, no statistically significant benefit was seen for fluoroquinolones (OR 1.20, 95% CI 0.48 to 3.0). In the randomized controlled trials, there were fewer adverse events that were mild, while one observational study suggested a higher risk of perforations in the fluoroquinolone group, a finding not corroborated in other studies.

The second review included 16 randomized controlled trials (1823 participants) that compared different topical antibiotics for the treatment of bacterial keratitis (*6*). No statistically significant difference in treatment success, time to cure or serious complications (including corneal perforation) between the groups was identified. Fluoroquinolones were found to be better tolerated in terms of ocular discomfort and chemical conjunctivitis than aminoglycoside–cephalosporin combinations (RR 0.20, 95% CI 0.10 to 0.41). However, fluoroquinolones increase the risk of corneal precipitates compared with the aminoglycoside–cephalosporin combinations (RR 24.4, 95% CI 4.68 to 126.9).

Endophthalmitis

No systematic reviews could be identified.

Guidelines (from the application)

The application presented the results of a search for clinical practice guidelines on the use of antibiotics for ocular infections.

Conjunctivitis

Five clinical practice guidelines were identified (*7–11*). The guideline by Azari and Barney, based on a systematic review of conjunctivitis diagnosis and treatment, mentions several options for management of uncomplicated bacterial conjunctivitis: no treatment, delayed treatment, or immediate antibiotic treatment (*7*). The likely benefits of treatment are: shorter duration of symptoms; decrease in transmissibility; and earlier return to school. If a decision is made to treat, any broad-spectrum antibiotic eye drops can be viewed as equally effective (e.g. aminoglycosides, fluoroquinolones, macrolides and sulfonamides) given the lack of direct comparisons.

The Médecins Sans Frontières guideline recommends cleaning eyes four times daily with boiled water with 0.9% sodium chloride, and to apply 1% tetracycline eye ointment twice daily for 7 days for suspected bacterial conjunctivitis, i.e. where there is abundant and purulent secretions, eyelids stuck together and unilateral at onset (*8*).

The Conjunctivitis Preferred Practice Pattern® of the American Academy of Ophthalmology recommends considering topical agents for mild bacterial conjunctivitis, and obtaining a swab to guide targeted topical treatment given that methicillin-resistant *S. aureus* is a more frequently detected pathogen in severe conjunctivitis (*9*). No specific antibiotics are recommended because of the lack of data on benefit of one antibiotic over another. For trachoma, the guideline recommends either a single dose of azithromycin 1 g orally or doxycycline 100 mg twice daily for 7 days.

The Australian guideline on the management of *C. trachomatis* eye infection recommends a single dose of azithromycin at 20 mg/kg body weight up to 1000 mg (*10*). Bhosai et al. also recommend the use azithromycin with the same single dose for the treatment of trachoma (*12*). The use of topical tetracycline ointment was discouraged because of adherence concerns. This is in keeping with a WHO guideline published in 2016 that was not formally included in this review as the guideline covers the entire spectrum of *C. trachomatis* infections and only touches briefly on trachoma (*11*).

Keratitis

Two clinical practice guidelines on this topic were identified (*13*, *14*). The United Kingdom College of Optometrists guideline on management of microbial keratitis recommends monotherapy with either topical levofloxacin or moxifloxacin, and to add (unspecified) systemic antibiotics if the lesion is close to the limbus (*13*). The Royal Victorian eye and ear hospital guideline on

the management of microbial keratitis recommends the use of hourly topical fluoroquinolones (ofloxacin 3 mg/mL) at least for the first 48 hours and then to reduce the frequency gradually (*14*).

Endophthalmitis

Guidelines published by the United Kingdom College of Optometrists focused specifically on postsurgical endophthalmitis (*15*). No specific antibiotics are recommended and only general recommendations for management are provided (including the use of unspecified topical and systemic antibiotics).

A guidance document by the American Academy of Ophthalmology on endogenous endophthalmitis recommends a wide spectrum of possible systemic antibiotics depending on the (suspected) pathogen that have a good penetration into the vitreous humour, for example, aminoglycosides, clindamycin, fluoroquinolones, and third-generation cephalosporins (*16*). Options for intravitreal therapy in the guidance, if indicated, include ceftazidime (2.25 mg/0.1 mL) and vancomycin (1.0 mg/0.1 mL). Amikacin (0.4 mg/0.1 mL) and clindamycin (1.0 mg/0.1 mL) are suggested as alternative antibiotics if the primary regimen cannot be used.

Rationale for antibiotic selection (from the application)

Conjunctivitis

If bacterial conjunctivitis is suspected, treatment with topical antibiotics is indicated for moderate to severe infection and can also be considered in mild cases. No specific topical antibiotic can be recommended because of the lack of direct comparisons; therefore, the choice for empiric antibiotics should be based on local availability. Topical antibiotics containing fluoroquinolone are proposed (e.g. ofloxacin).

For trachoma, the treatment of choice is oral azithromycin as a single dose of 1 g (or 20 mg/kg body-weight in children) because of the potentially better efficacy and adherence with the single-dose regimen.

Keratitis

Topical fluoroquinolones (e.g. ofloxacin) are recommended for (suspected) bacterial keratitis. As there are no recommendations for specific agents, the choice depends on local availability. Antibiotics should be adjusted based on culture results, if possible. Adding systemic antibiotics should be considered in addition to topical antibiotics if the lesion is close to the limbus. However, no recommendation can be made on the type of systemic antibiotic.

Endophthalmitis

No specific recommendations can be made given the lack of systematic reviews and the non-specific recommendations in the guidelines identified. Empiric

antibiotic choice must target the most common pathogens (Gram-positive bacteria). For systemic treatment, given the range of pathogens, ceftriaxone plus vancomycin are proposed. For intravitreal administration, vancomycin and ceftazidime are proposed.

Committee considerations (e.g. additional evidence, dose/duration, costs)

Not applicable

EML listings

Topical ophthalmological antibacterial medicines currently included in the Model Lists are summarized below.

Medicine	Formulation and strength	Indication
Azithromycin	Eye drops 1.5%	Trachoma
Erythromycin	Ointment 0.5%	Infections due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*
Gentamicin	Eye drops 0.3%	Blepharitis, conjunctivitis
Ofloxacin	Eye drops 0.3%	Infectious keratitis
Tetracycline	Ointment 1%	Blepharitis, conjunctivitis, infectious keratitis, trachoma

Oral azithromycin is currently included in the Model Lists as a systemic single-dose treatment for trachoma. Ceftazidime and ceftriaxone and vancomycin are included in the Model Lists for other indications.

Committee recommendations

The Expert Committee noted that infections of the eye and surrounding structures are frequent around the world and are an important cause of blindness. Given increasing concerns about overuse of antibiotics, the emergence of antimicrobial resistance and the need to guarantee prompt access to highly beneficial treatments, the Expert Committee noted the importance of revising and updating the Model Lists to provide clear information on the use of antibiotics in ocular infections.

With regard to conjunctivitis, topical anti-infective medicines currently included on the Model Lists are gentamicin and tetracycline (each with a square box). The Committee noted that based on the evidence and guidelines reviewed in the application, topical antibiotics are indicated for moderate to severe infection and can be considered in mild cases. The available evidence does not make it possible to identify specific, preferred antibiotics for this indication. The Committee therefore endorsed the current listings for gentamicin and

tetracycline, and recommended that the indications for ofloxacin be expanded to include the treatment of conjunctivitis. For trachoma, a specific type of conjunctivitis caused by certain serovars of *C. trachomatis*, the treatment of choice is a single oral dose of azithromycin. Topical azithromycin or topical tetracycline are also indicated. The Committee also endorsed the current listings on the EML and EMLc for oral and topical azithromycin and for topical tetracycline for the treatment of trachoma.

For infectious keratitis, topical anti-infective medicines currently included on the Model Lists are ofloxacin and tetracycline (each with a square box). The Committee noted that based on the evidence and guidelines reviewed in the application, topical fluoroquinolones are indicated for infectious keratitis. The Committee therefore endorsed the current square box listing for ofloxacin for this indication. No change was recommended for the listing of tetracycline. The Committee noted that systemic antibiotics may be indicated in certain situations (e.g. with lesions close to the limbus) but the available evidence could not identify specific, preferred antibiotics. The Committee therefore did not endorse listing for systemic antibiotics for infectious keratitis.

For endophthalmitis, the Committee acknowledged the lack of high-quality evidence for antibiotic choice and specific recommendations in guidelines. Based on common practice and the range of pathogens, the application proposed ceftriaxone plus vancomycin for systemic treatment, and vancomycin and ceftazidime by intravitreal administration for the empiric treatment of bacterial endophthalmitis. The Committee acknowledged that intravitreal treatment requires specialist training and adequate infrastructure to ensure safe administration. Given that bacterial endophthalmitis is a serious, sight-threatening infection, the Expert Committee recommended the current listings for ceftazidime, ceftriaxone and vancomycin be extended to include the indication of bacterial endophthalmitis as first-choice treatment options.

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Antibiotics for necrotizing fasciitis – new indication – EML and EMLc

Ceftriaxone	**ATC Code: J01DD04**
Clindamycin	**ATC Code: J01FF01**
Metronidazole	**ATC Code: J01XD01/P01AB01**
Piperacillin + tazobactam	**ATC Code: J01CR05**
Vancomycin	**ATC Code: J01XA01**

Proposal

Extension of the indications for ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin to include treatment of necrotizing fasciitis, specifically:

- The combination of piperacillin + tazobactam and clindamycin for empiric treatment of necrotizing fasciitis
- The combination of ceftriaxone with metronidazole for treatment of necrotizing fasciitis after *Streptococcus pyogenes* has been ruled out as the causative pathogen
- The combination of vancomycin with one of the above-mentioned options for treatment of necrotizing fasciitis if methicillin-resistant *Staphylococcus aureus* is suspected as the causative pathogen.

Applicant

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Global Coordination and Partnership (Division of Antimicrobial Resistance)
Surveillance, Prevention and Control (Division of Antimicrobial Resistance)

EML/EMLc

EML and EMLc

Section

6.2.1 Access group antibiotics (clindamycin, metronidazole)
6.2.2 Watch group antibiotics (piperacillin + tazobactam, ceftriaxone, vancomycin)

Dose form(s) & strength(s)

Dose forms and strengths as currently listed on the EML and EMLc, plus additional new strength intravenous formulations for ceftriaxone, clindamycin and vancomycin on the EML to better meet the dosing needs of adults for this indication.

Ceftriaxone: powder for injection 2 g
Clindamycin: injection 600 mg/4 mL and 900 mg/6 mL
Vancomycin: powder for injection 500 mg and 1 g

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin are currently included in the EML and EMLc for multiple other indications.

A review of antibiotic treatment for skin and soft tissue infections was prepared by the Department of Health Research Methods, Evidence and Impact, McMaster University, Canada and was considered by the Expert Committee in 2017. The Committee recommended listing amoxicillin + clavulanic acid, cloxacillin and cefalexin for the treatment of mild skin and soft-tissue infections. The antibiotics proposed in the application for severe skin and soft-tissue infections (including necrotizing fasciitis) were not recommended because the Committee chose to focus on the empirical treatment of common mild to moderate community-acquired infections (*1*).

Public health relevance (burden of disease)

Necrotizing fasciitis is a rare infection, but it is associated with significant morbidity and mortality, especially in cases of delayed diagnosis and treatment. The disease is caused mostly by bacteria and is characterized by acute and fulminant necrosis with tissue destruction and signs of systemic toxicity. Risk factors for necrotizing fasciitis include traumatic and surgical wounds, especially in patients with diabetes, peripheral vascular disease or immunosuppression (*2*). However, necrotizing fasciitis can also occur in otherwise healthy people irrespective of their age. Necrotizing fasciitis is very rare in children but may occur as a complication of varicella (chickenpox) or in the context of a compromised immune system.

Few data are available on time trends in the epidemiology of necrotizing fasciitis. In the USA, over a 10-year period (2003–2013), an estimated 9871 deaths related to necrotizing fasciitis occurred, corresponding to a mortality rate of 4.8 per million person-years (*3*). In an Asian study, an overall annual incidence of 3.2 hospitalizations per 100 000 person-years was reported between 2002 and 2011 (4). Other studies report an incidence that ranges from 0.3 to 15 cases per 100 000 population (*2*, *5*, *6*). Among all invasive *Streptococcus pyogenes* infections, necrotizing fasciitis represents only a minority of cases – about 7% for all ages combined in one study of surveillance data in the USA (*7*).

Summary of evidence: benefits (from the application)

The 2017 McMaster review of systematic reviews, meta-analyses and guidelines published between 1996 and 2016 for antibiotics for skin and soft tissue infections included evidence for antibiotic treatment of severe skin and soft tissue infections, and is summarized in the report of the 2017 Expert Committee meeting (*1*). Since no important new evidence on antibiotic therapeutic options for this infection has become available since then, the evidence presented in 2017 still reflects the current evidence base.

The 2017 review included the 2014 guidelines of the Infectious Diseases Society of America on skin and soft tissue infections, which cover both paediatric and adult patients (*8*). These guidelines included the following recommendations for necrotizing infections of the skin, fascia and muscle: (i) piperacillin + tazobactam plus vancomycin; (ii) a carbapenem (meropenem, imipenem, ertapenem), or (iii) cefotaxime plus metronidazole or clindamycin. Antibiotics, including cefazolin, ceftriaxone, clindamycin, daptomycin, doxycycline, linezolid, penicillin G, quinupristin + dalfopristin, semi-synthetic penicillins (nafcillin, oxacillin) and vancomycin, and are listed as options for specific pathogens such as Streptococcus, *Staphylococcus aureus*, *Clostridium* species, *Aeromonas hydrophila* and *Vibrio* infections.

In the context of the 2017 McMaster review, ceftriaxone, clindamycin, meropenem, metronidazole, piperacillin + tazobactam and vancomycin were proposed as treatment options for severe skin and soft tissue infections (including necrotizing fasciitis) for inclusion on the Model Lists. The Expert Committee did not recommend them because it decided to prioritize listing of antibiotics for mild, community-acquired infections. Therefore, the Expert Committee's decision was not a reflection of its evaluation of the evidence for benefit for these antibiotics in the treatment of necrotizing fasciitis.

Summary of evidence: harms (from the application)

Ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin are already included in the EML and EMLc. They are widely used for many different types of infection and potential side-effects when used for

the treatment of necrotizing fasciitis do not differ from those encountered when these antibiotics are used for a different indication. Given the severity of necrotizing fasciitis and the high mortality associated with delays in treatment, the benefits of adequate antibiotic treatment outweigh the potential side-effects of each individual antibiotic.

Additional evidence (not in the application)

Not applicable

WHO guidelines

There are no WHO guidelines for the management of severe skin and soft tissue infections and necrotizing fasciitis.

Costs/cost–effectiveness

As the proposed medicines are already included on the Model Lists and on many national essential medicine lists, a review of the comparative costs and cost–effectiveness was not done.

Availability

Ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin have regulatory approval globally and generic varieties are available.

Other considerations

Following the principles of antimicrobial stewardship, meropenem has not been generally recommended as an option for the empiric treatment of clinical infections. Wide use of empiric treatment with meropenem has been associated with selection of carbapenem resistance at both a patient and hospital level. Recommendations for the use of meropenem have generally been limited to where a patient is known to be infected or colonized with a multidrug-resistant pathogen that is resistant to other recommended antibiotics.

Committee recommendations

The Expert Committee noted that necrotizing fasciitis is a rare but severe skin and soft tissue infection that is associated with significant morbidity and mortality, especially in cases of delayed diagnosis and treatment.

The Committee noted the previous decision not to include empiric antibiotic treatment for severe skin and soft tissue infections, and to focus rather on mild, community-acquired infections. However, given the serious consequences of delayed treatment in necrotizing fasciitis, the Committee considered recommendations for empiric antibiotic therapy would be beneficial from both a clinical and public health perspective.

The Expert Committee reviewed the antibiotics proposed for listing for necrotizing fasciitis in the 2017 application and recommended expanding the indications for ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin on the EML and EMLc to include them as first-choice treatment options for treatment of necrotizing fasciitis as proposed in the application, including the addition of new intravenous formulations of ceftriaxone 2 g, clindamycin 600 mg and 900 mg, and vancomycin 500 mg and 1 g.

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Antibiotics for neonatal meningitis – new indication – EMLc

Gentamicin — ATC Code: J01GB03

Proposal

Extension of the indications for gentamicin on the EMLc to include treatment of acute bacterial meningitis in neonates.

Applicant

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Global Coordination and Partnership (Division of Antimicrobial Resistance)

EML/EMLc

EMLc

Section

6.2.1 Access group antibiotics

Dose form(s) & strength(s)

Dose forms and strengths as currently listed on the EMLc

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Gentamicin is currently included in the EML and EMLc for multiple other indications. The combination of gentamicin and a beta-lactam is listed as first choice for: acute malnutrition in infants, children or adolescents; severe community-acquired pneumonia in children; and sepsis in neonates and children. Gentamicin is also listed as second choice for surgical prophylaxis in children and adults, and for gonococcal infection.

Reviews of the evidence for empiric antibiotic treatment options for meningitis and sepsis (not limited to neonates) had been prepared by the Department of Health Research Methods, Evidence and Impact, McMaster

University, Canada, and were considered by the Expert Committee in 2017 (*1*). The evidence assessed in the 2017 reviews forms the basis for the current application.

Public health relevance (burden of disease)

Neonatal meningitis occurs worldwide and, according to estimates by WHO and the Maternal and Child Epidemiology Estimation group, 14% of all neonatal deaths in 2017 were due to meningitis or sepsis (these two syndromes usually overlap and it is often impossible to separate the two clinically) (*2*). The 2016 Global Burden of Disease study estimated that almost 20 000 neonates (i.e. children < 1 month of age) died of meningitis in 2016. However, authors of the Global Burden of Disease study acknowledged that the diagnosis is difficult and this could result in an underestimation of the burden of disease of neonatal meningitis *(*3). In general, the incidence and mortality of meningitis are higher in resource-constrained countries.

Risk factors for neonatal meningitis include preterm birth, low birth weight, maternal peripartum infections or and delivery-associated risk factors such as prolonged rupture of membranes or traumatic delivery (*4*). The causative pathogens differ from those commonly found in older children and adults with infectious meningitis. *Streptococcus agalactiae* (a group B streptococci) and *Escherichia coli* are the most frequent bacteria causing neonatal meningitis. *Streptococcus agalactiae* is still the most frequent cause of neonatal meningitis despite a decline in cases over the years in settings where maternal screening and intrapartum antibiotic prophylaxis of mothers with a positive screening test for group B streptococcus is done as part of prenatal care. *Streptococcus pneumoniae* and *Listeria monocytogenes*, bacteria commonly encountered in meningitis in older children and adults, are also pathogens in neonatal meningitis (*5*).

Summary of evidence: benefits (from the application)

The clinical presentations of neonatal sepsis and neonatal meningitis overlap and are difficult to differentiate. The 2017 McMaster review of systematic reviews, meta-analyses and guidelines published between 1996 and 2016 included studies on sepsis in children < 5 years. This evidence is considered relevant for neonatal meningitis.

Systematic reviews and meta-analyses

Two Cochrane systematic reviews were included in the McMaster review (*6*,*7*). The first (two randomized controlled trials, 127 participants) compared single to combination regimens for suspected early neonatal sepsis, but results on 28-day mortality were indeterminate because of the small sample size (risk ratio (RR) 0.75, 95% confidence interval (CI) 0.19 to 2.9) (*6*). The second systematic review examined antibiotic regimens for late onset sepsis in neonates (one randomized

controlled trial, 24 participants) and compared beta-lactams alone with beta-lactams combined with aminoglycosides. The results were also inconclusive (RR 0.17 for mortality before discharge, 95% CI 0.01 to 3.23; the same as the results for treatment failure) because of the small sample size (*7*).

Guidelines

The 2012 United Kingdom clinical guidelines on antibiotics for the prevention and treatment of early-onset neonatal infection advise using intravenous benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless local bacterial resistance patterns suggest using a different antibiotic (*8*). These guidelines were updated in April 2021 and have kept the same recommendations (*9*).

Although not formally a guideline, a policy report by the Committee on Fetus and Newborn of the American Academy of Pediatrics published in 2012 recommends ampicillin and an aminoglycoside (usually gentamicin), for treatment of infants with suspected early-onset sepsis (*10*). If Gram-negative meningitis is diagnosed, cefotaxime in combination with an aminoglycoside is recommended. The 2018 update, has kept the combination of ampicillin and gentamicin as the first choice for the empiric treatment of early-onset sepsis (*11*).

Summary of evidence: harms (from the application)

The harms and toxicities of gentamicin are well known and have been reviewed extensively by the Expert Committee on previous occasions. Gentamicin has been included on the EML since 1977 and on the EMLc since 2007.

Additional evidence (not in the application)

Not applicable

WHO guidelines

Several WHO documents provide guidance on the management of neonatal meningitis/sepsis and recommend gentamicin in combination with a beta-lactam (ampicillin, ceftriaxone or cefotaxime) for empiric treatment.

The 2017 WHO recommendations on newborn health (*12*) includes the following recommendations for the choice of empiric antibiotics for suspected neonatal sepsis or serious bacterial infections when referral is not feasible.

- Neonates with signs of sepsis should be treated with ampicillin (or penicillin) and gentamicin as the first-line antibiotic treatment for at least 10 days. (Strong recommendation, low quality of evidence).
- Young infants 0–59 days old with clinically evident severe infection when referral is not feasible:

- Option 1: Intramuscular gentamicin 5–7.5 mg/kg (for low-birth-weight infants, gentamicin 3–4 mg/kg) once daily for 7 days, and twice daily oral amoxicillin, 50 mg/kg per dose for 7 days. Close follow-up is essential. (Strong recommendation, moderate quality of evidence).
- Option 2: Intramuscular gentamicin 5–7.5 mg/kg (for low-birth-weight infants, gentamicin 3–4 mg/kg) once daily for 2 days, and twice daily oral amoxicillin, 50 mg/kg per dose for 7 days. Close follow-up is essential. A careful assessment on day 4 is essential. (Strong recommendation, low quality of evidence).

The 2015 WHO guideline for managing serious bacterial infection in young infants when referral is not feasible (*13*) includes the following recommendations:

Young infants 0–59 days old who have any sign of critical illness (at presentation or developed during treatment of severe clinical infection) should be hospitalized after prereferral treatment with antibiotics. (Strong recommendation, very low-quality evidence (standard of care)).

Although no comparative trials are available showing the relative efficacy and safety of treatments, in cases where hospitalization is not possible at all, critically ill children should be given one of the following treatment regimens until hospitalization becomes possible (up to 7 days):

- twice daily intramuscular ampicillin and once daily intramuscular gentamicin
- once daily intramuscular ceftriaxone with or without once daily intramuscular gentamicin
- twice daily intramuscular benzylpenicillin and once daily intramuscular gentamicin
- once daily intramuscular procaine benzylpenicillin and once daily intramuscular gentamicin.

The 2013 *WHO pocket book of hospital care for children* (*14*) includes the following recommendations for treatment of meningitis in neonates.

- The first-line antibiotics are ampicillin and gentamicin for 3 weeks. Alternatively, give a third-generation cephalosporin, such as ceftriaxone or cefotaxime, and gentamicin for 3 weeks.
- The proposed dose and duration for the empiric treatment of neonatal meningitis is:
  - Ampicillin (intravenous/intramuscular) 50 mg/kg per dose, twice a day (1st week of life), 50 mg/kg per dose, three times a day (> 1st week of life) in combination with gentamicin (intravenous/

intramuscular) 5 mg/kg per dose once a day (1st week of life), 7.5 mg/kg once a day (after 1st week of life).

- If ampicillin is unavailable alternative options are ceftriaxone 50–100 mg/kg per dose, once a day, or cefotaxime 50 mg/kg per dose, twice a day (1st week of life) and three times a day (after 1st week of life).

- Treatment duration: 3 weeks if no pathogen is isolated.

Costs/cost–effectiveness

As gentamicin is already included on the Model Lists and in many national essential medicine lists, a review of the comparative costs and cost-effectiveness has not been undertaken for the current application.

Availability

Gentamicin has regulatory approval globally and is widely available

Other considerations

Not applicable

Committee recommendations

The Committee noted that sepsis and meningitis are responsible for a substantial proportion of global neonatal mortality, and that the availability of empiric antibiotic treatment options is critical to reduce this burden. Gentamicin is currently included on the EMLc for the treatment of neonatal sepsis.

The Committee noted that gentamicin, in combination with a beta-lactam, is recommended as first-line treatment of suspected or proven neonatal meningitis in several WHO and other international guidelines.

To ensure alignment of the EMLc with these recommendations, the Expert Committee therefore recommended extending the indications for gentamicin on the EMLc to include empiric antibiotic treatment of neonatal meningitis as a first-choice option. The Committee recognized the importance of the availability of lower strength formulations of gentamicin for the dosing of paediatric patients.

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Antibiotics for intra-abdominal infections in children – new indication – EMLc

Ampicillin	**ATC Code: J01CA01**
Gentamicin	**ATC Code: J01GB03**

Proposal

Extension of the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections in neonates and children.

Applicant

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EML/EMLc

EMLc

Section

6.2.1 Access group antibiotics

Dose form(s) & strength(s)

Dose forms and strengths as currently listed on the EMLc

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Ampicillin and gentamicin are currently included in the EML and EMLc for multiple other indications. The combination of ampicillin and gentamicin is listed as first choice for: acute malnutrition in infants, children or adolescents; severe community-acquired pneumonia in children; and sepsis in neonates and children. Ampicillin is also listed as second choice for the treatment of acute bacterial meningitis in children and adults, and gentamicin is also

listed as second choice for surgical prophylaxis in children and adults, and for gonococcal infection.

Inclusion of ampicillin and gentamicin for the treatment of intra-abdominal infections in children will align the EMLc with current WHO guidance documents, in particular with the *Pocket book of hospital care for children* (*1*).

Public health relevance (burden of disease)

Community-acquired intra-abdominal infections occur in children worldwide and are caused by a variety of conditions, the most frequent of which are acute appendicitis and intestinal perforation occurring as a complication of enteric fever in endemic settings (*2*). Acute appendicitis is particularly frequent in children (*3*) and most cases (70%) are uncomplicated and with a very low short-term postappendectomy mortality (1%) However, the incidence of appendicitis varies across settings; while a decrease has been observed in western Europe and North America since the 1990s, increasing trends are reported in Asia, South America and the Middle East (*4*).

Summary of evidence: benefits (from the application)

Both ampicillin and gentamicin are commonly used in neonates and children and the evidence of benefits has already been extensively revised by the EML Working Group and Expert Committee.

In the context of the review of antibacterial medicines undertaken for the 2017 EML update, aminoglycosides were identified as alternative, targeted treatment options to the core antibiotics listed for complicated intra-abdominal infections, based on local resistance data. The review noted that ampicillin could be considered as a treatment option if additional enterococcal coverage is needed, e.g. because the regimen used would otherwise not be covering *Enterococcus* spp. (e.g. ceftriaxone plus metronidazole). Since the systematic reviews gave inconclusive results, the treatment options proposed for adults and children were based on the review of national and international guidelines, notably the 2010 Infectious Diseases Society of America/Surgical Infection Society guidelines (*5*) and the guidelines developed at the 2010 consensus conference of the World Society of Emergency Surgery (*6*). In 2017, the Surgical Infection Society revised the 2010 guidelines (without Infectious Diseases Society of America collaboration) (*7*). The revised guidelines confirmed aminoglycoside-based regimens for neonates; in particular, the guidelines say, "Use ampicillin, gentamicin, and either metronidazole or clindamycin; ampicillin, cefotaxime, and either metronidazole or clindamycin; or meropenem in paediatric patients less than one month of age (45 weeks postconceptional age)" (*7*).

Summary of evidence: harms (from the application)

The evidence of harms and toxicity has already been extensively reviewed by the EML Working Group and Expert Committee and a separate review was not done for this application.

No additional evidence has emerged that would discourage use of ampicillin and gentamicin for treatment of intra-abdominal infections in neonates and children.

Additional evidence (not in the application)

Not applicable

WHO guidelines

The *WHO Pocket book of hospital care for children* includes the following recommendations for treatment of intra-abdominal infections in children (*1*).

- Appendicitis: Give antibiotics once the diagnosis is established: ampicillin (25–50 mg/kg intramuscular or intravenous four times a day), gentamicin (7.5 mg/kg intramuscular or intravenous once a day) and metronidazole (10 mg/kg intravenous or oral three times a day).
- Necrotizing enterocolitis: Start antibiotics and give ampicillin (or penicillin) plus gentamicin plus metronidazole for 10 days.

The WHO recommendations on newborn health recommend that young neonates with suspected necrotizing enterocolitis should be treated with intravenous or intramuscular ampicillin (or penicillin) and gentamicin as first-line antibiotic treatment for 10 days. (Strong recommendation, low quality of evidence) (*8*).

Costs/cost–effectiveness

As the proposed medicines are already included on the Model Lists and on many national essential medicine lists, a review of the comparative costs and cost–effectiveness was not done.

Availability

Ampicillin and gentamicin have regulatory approval globally and are widely available in brand and generic forms.

Other considerations

Not applicable

Committee recommendations

The Committee noted that ampicillin and gentamicin are recommended as treatment options for complicated intra-abdominal infections in children in several WHO and other international guidelines. In addition, there is extensive clinical experience using ampicillin and gentamicin, usually combined with metronidazole, for this indication in the paediatric population.

To ensure alignment of the EMLc with these recommendations, the Expert Committee therefore recommended extending the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections in children, as first-choice treatment options.

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Amoxicillin – remove indication – EML and EMLc

Amoxicillin **ATC Code: J01CA04**

Proposal

Removal of the indication of treatment of lower urinary tract infections from the listings of amoxicillin on the EML and EMLc.

Applicant

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Global Coordination and Partnership (Division of Antimicrobial Resistance)
Surveillance, Prevention and Control (Division of Antimicrobial Resistance)

EML/EMLc

EML and EMLc

Section

6.2.1 Access group antibiotics

Dose form(s) & strength(s)

Not applicable

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Amoxicillin was recommended as a first-choice treatment option for empiric treatment of lower urinary tract infections in adults and children in 2017, as part of the comprehensive review of antibiotics for common infectious syndromes (*1*).

The EML and EMLc currently include alternative first-choice treatment options for lower urinary tract infection (nitrofurantoin, sulfamethoxazole + trimethoprim, amoxicillin + clavulanic acid, and single-agent trimethoprim).

Public health relevance (burden of disease)

Lower urinary tract infections are very common worldwide and can affect people of any age. According to the Global Burden of Disease study, in 2017 for all ages and both sexes combined, an estimated 274 million new cases of urinary tract infections (lower and upper) occurred globally (*2*). The incidence of urinary tract infections is highest in women and increases with age and frequency of sexual activity. However, after 65 years of age, rates of lower urinary tract infections in men and women tend to be more similar (*3*).

Summary of evidence: benefits (from the application)

Evidence supporting the requested change relies on data from a 2020 report by the Global Antimicrobial Resistance Surveillance System (GLASS) on global antimicrobial resistance (*4*). GLASS data from 22 countries indicate that a median of 75% (range 45–100%) of *Escherichia coli* urinary isolates are resistant to amoxicillin.

In addition, the empiric use of amoxicillin for treatment of lower urinary tract is explicitly discouraged in multiple guidelines because of high rates of antimicrobial resistance to amoxicillin (*5–7*).

GLASS data are not reported for amoxicillin + clavulanic acid or nitrofurantoin. However, several sources indicate that susceptibility of *E. coli* in urinary isolates remains generally high, in both adults and children (*8–10*). GLASS data indicate a median of 55% (range 40–70%) of *E. coli* urinary isolates are resistant to sulfamethoxazole + trimethoprim (*4*).

Summary of evidence: harms (from the application)

Not applicable

Additional evidence (not in the application)

Not applicable

WHO guidelines

Not applicable

Costs/cost–effectiveness

No applicable

Availability

Not applicable

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted the recent data from the Global Antimicrobial Resistance Surveillance System which indicate very high levels of resistance to amoxicillin of *E. coli* in urinary tract infections, and that for this reason the empiric use of amoxicillin for treatment of lower urinary tract infections is now discouraged in multiple international treatment guidelines.

The Committee therefore recommended that the indication of treatment of lower urinary tract infections be removed from the listings of amoxicillin on the EML and EMLc.

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1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1006; https://apps.who.int/iris/handle/10665/259481, accessed 13 August 2021).
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Amoxicillin + clavulanic acid – new formulation – EML

Amoxicillin + clavulanic acid **ATC Code: J01CR02**

Proposal

Inclusion of a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults.

Applicant

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EML/EMLc

EML

Section

6.2.1 Access group antibiotics

Dose form(s) & strength(s)

Tablet: 875 mg + 125 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Amoxicillin + clavulanic acid, in multiple formulations, has been included on the Model Lists since 1997. Amoxicillin + clavulanic acid is currently included on the EML and EMLc as a first- or second-choice empiric treatment for several bacterial infections.

The EML currently recommends amoxicillin + clavulanic acid as a second-choice option for community-acquired pneumonia because in most cases there is no need to broaden the spectrum of antibacterial activity to cover more resistant pathogens and amoxicillin (or phenoxymethylpenicillin) can

safely be used. The other reason is that amoxicillin + clavulanic is associated with more frequent side-effects than amoxicillin alone – mostly diarrhoea, including *Clostridioides difficile* infection (*1*).

Amoxicillin + clavulanic acid is also recommended in the EML as a first-choice option for the empiric treatment of mild, community-acquired intra-abdominal infections in patients who are not critically ill and there is no suspicion of sepsis or septic shock.

Public health relevance (burden of disease)

Community-acquired pneumonia is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (*2*). According to the Global Burden of Disease study, in 2017 among all ages and sexes combined, an estimated 471 million new cases of lower respiratory tract infections (including community-acquired pneumonia) occurred globally (*3*). The most common causative pathogen worldwide is *Streptococcus pneumoniae*, and viral co-infection is not unusual. In general, the incidence of community-acquired pneumonia and risk of death increase with age (*4*). Community-acquired pneumonia is curable and preventable. Most people who develop this infection can be successfully treated with a 5-day antibiotic regimen. Vaccines to prevent community-acquired pneumonia caused by certain pathogens (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and influenza virus).

Intra-abdominal infections include uncomplicated infections with no involvement of the peritoneal cavity and no abscess formation and complicated infections with involvement of the peritoneal cavity and/or abscess formation. The most frequent intraabdominal infections include acute appendicitis, acute cholecystitis, acute cholangitis, acute diverticulitis and pyrogenic liver abscess. Treatment of these infections usually requires a combination of antibiotics and surgery to achieve adequate control of the source of infection.

Summary of evidence: benefits (from the application)

The rationale for the inclusion of the 875 mg + 125 mg formulation of amoxicillin + clavulanic acid is to increase the amoxicillin to clavulanic acid ratio from 4:1 (500 mg + 125 mg formulation) to 7:1. There is limited evidence about differences in clinical and microbiological efficacy of the different ratios of amoxicillin to clavulanic acid. However, the advantage of the 7:1 ratio formulation is increased exposure to amoxicillin without increased exposure to clavulanic acid. The reason for limiting exposure to clavulanic acid is that increasing its dose exposes patients to a higher risk of gastrointestinal side-effects (especially diarrhoea) with only a minimal increase in efficacy against beta-lactamases (*5*).

Amoxicillin + clavulanic acid is recommended for the treatment of mild community-acquired pneumonia because it is effective against the most

likely bacterial pathogens responsible for this syndrome (notably *Streptococcus pneumoniae* and *Haemophilus influenzae*, including strains that produce beta-lactamases) and because it is safe, inexpensive and readily available in many settings. In general, amoxicillin alone remains effective against Streptococcus pneumoniae isolates in most cases because these isolates are not known to produce beta-lactam enzymes (*5*). However, other pathogens (mostly *Haemophilus influenzae*) produce beta-lactamases in a large proportion of cases (*6*, *7*) and could therefore be resistant to amoxicillin alone. Such cases would therefore benefit from treatment with amoxicillin + clavulanic acid.

A key element of the treatment of community-acquired pneumonia is to maximize the chance of bacterial eradication in order to achieve clinical success and to reduce the risk of resistance developing. For beta-lactam agents, maximal clinical efficacy depends on the time that the plasma concentration of the drug remains above the level of the minimal inhibitory concentration (MIC) for the target pathogen (T>MIC). For amoxicillin, a T>MIC of at least 30–40% between dosing intervals is required to effectively treat most pathogens responsible of mild community-acquired pneumonia. Therefore, the advantage of a formulation with a higher dose of amoxicillin is that it can improve the efficacy of amoxicillin + clavulanic acid for the treatment of pathogens with higher MICs (*8*). In particular, the 875 mg +125 mg formulation (given three times a day) would achieve bacteriological efficacy against strains with amoxicillin MICs of up to 4 mg/L (T>MIC 34% for MICs of 4 mg/L, 57% for MICs of 2 mg/L and 69% for MICs of 1 mg/L), while the 500 mg + 125 mg formulation (three times a day) would only achieve bacteriological efficacy against strains with MICs of up to 2 mg/L (T>MIC 43% for MICs of 2 mg/L and 55% for MICs of 1 mg/L) (*9*). An additional advantage of amoxicillin + clavulanic acid that applies to both its use for the treatment of mild community-acquired pneumonia and mild community-acquired intra-abdominal infections is its lower potential for resistance compared with other antibiotic options that are sometimes used for the treatment of these syndromes, most notably fluoroquinolones. In patients with community-acquired pneumonia, amoxicillin + clavulanic acid is a particularly valid option in patients who would be at higher risk of poor outcomes if initial empiric treatment were inadequate (e.g. patients with multiple comorbidities who are often more vulnerable to infections or patients with a higher risk of resistant infections due to frequent antibiotic exposure). The clinical and bacteriological efficacy of the 875 mg +125 mg formulation is high (> 90% for clinical efficacy and 80–90% for microbiological efficacy at the end of treatment in trials where this formulation has been used (*10*)) including in settings with a high prevalence of penicillin-resistant *Streptococcus pneumoniae* (*11*).

Many patients with intra-abdominal infections may not be able to tolerate oral treatment in the initial phase of treatment, especially those with complicated infections that require surgery; therefore, patients are often started

on intravenous treatment. For the treatment of intra-abdominal infections, the use of the 875 mg +125 mg oral formulation of amoxicillin + clavulanic would apply in only certain circumstances: initial empiric treatment of mild cases in patients who can tolerate oral treatment (e.g. patients managed in the outpatient setting) and intravenous to oral switch to complete the course of treatment initiated with intravenous therapy.

Amoxicillin + clavulanic acid has a range of antibacterial activity that allows for the coverage of the most likely pathogens responsible for intra-abdominal infections (most notably *Escherichia coli*, enteric streptococci and anaerobic bacteria) even though amoxicillin + clavulanic resistance rates among *E. coli* isolates may be of concern in some settings (*12*). No clinical trial was identified that directly compared the efficacy of different doses of oral amoxicillin + clavulanic acid for intra-abdominal infections. However, the 875 mg + 125 mg oral formulation has been used in several trials, especially for the treatment of uncomplicated acute appendicitis with antibiotics alone (*13*, *14*), while lower doses of amoxicillin + clavulanic acid (500 mg + 25 mg) are generally used when treatment is started intravenously and then later switched to oral treatment (*15*). As detailed above for community-acquired pneumonia, the use of a higher dose of amoxicillin in combination with clavulanic acid, improves efficacy for the treatment of pathogens with higher MICs; therefore, the 875 mg +125 mg is preferable to achieve cure and reduce the risk of resistance developing when oral treatment is chosen. In serious infections, such as intra-abdominal infections, high protein binding of beta-lactams and rapid elimination can reduce the amount of antibiotic available in both the plasma and tissue, increasing the risk of treatment failure, especially in cases of pathogens with higher MICs (*16*). Therefore, doses should be increased and the interval between doses reduced, especially when oral beta-lactam treatment is used. In order to appropriately treat resistant pathogens, the daily dose of amoxicillin can be more safely increased than the dose of other antibiotics used to treat intra-abdominal infections such as fluoroquinolones. Fluoroquinolones have a worse safety profile, both for gastrointestinal and mild neurological reactions (nausea, vomiting, dizziness, insomnia and headache) but also for more serious adverse events such as tendinitis and tendon rupture (*17*), risk of arrhythmias (*18*) or possibly rupture of an aortic aneurysm (*19*).

Summary of evidence: harms (from the application)

Potential harms associated with the 875 mg + 125 mg formulation of amoxicillin + clavulanic acid are not expected to differ from the 500 mg + 125 mg preparation, as the dose of clavulanic acid (responsible for common side-effects such as diarrhoea) remains the same. Moreover, in published trials, even higher doses of amoxicillin + clavulanic acid (2000 mg + 125 mg) have been safely used and were well tolerated (*10*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

Not applicable

Costs/cost–effectiveness

There are several suppliers of the 875 mg +125 mg formulation globally at a cost of about US$ 10 per pack (12 tablets) in high-income countries.

Availability

Amoxicillin + clavulanic acid 875 mg + 125 mg has regulatory approval globally and is available in most countries.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that the proposed formulation of amoxicillin + clavulanic acid will provide a higher dose of amoxicillin, without increasing the dose of clavulanic acid, and is particularly suitable for more unwell patients. In addition, the Committee noted that a higher ratio of amoxicillin to clavulanic acid is generally associated with less diarrhoea, a recognized adverse effect of this combination. The addition of this new formulation will also allow recommended amoxicillin doses to be achieved with a reduced pill burden for patients.

The Committee therefore recommended the addition of the new strength formulation of amoxicillin + clavulanic acid 875 mg + 125 mg tablets to the core list of the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults.

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Cefalexin – change indication – EML and EMLc

Cefalexin **ATC Code: J01DB01**

Proposal

Change to the listing of cefalexin for the indication of skin and soft tissue infections from a second-choice to first-choice empiric treatment option.

Applicant

Mark Loeb, Dominik Mertz; McMaster University, Hamilton, Canada
Veronica Zanichelli; WHO consultant

WHO technical department

Global Coordination and Partnership (Division of Antimicrobial Resistance)
Surveillance, Prevention and Control (Division of Antimicrobial Resistance)

EML/EMLc

EML

Section

6.2.1 Access group antibiotics

Dose form(s) & strength(s)

All dose forms and strengths of cefalexin currently listed

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Cefalexin was recommended as a second-choice treatment option on the EML and EMLc for empiric treatment of skin and soft tissue infections in adults and children in 2017, as part of the comprehensive review of antibiotics for common infectious syndromes (*1*). Amoxicillin + clavulanic acid and cloxacillin were recommended as first-choice treatment options because both provide good coverage against staphylococcal (non-methicillin-resistant *Staphylococcus aureus* (non-MRSA)) and streptococcal infections, which are the leading causes of mild to moderate community-acquired skin and soft-tissue infections worldwide.

Cefalexin was recommended as second-choice for when first-choice options are not available or in patients allergic to penicillin who can tolerate cephalosporins.

Public health relevance (burden of disease)

Bacterial skin infections occur worldwide and can affect all age groups; erysipelas is more frequent in children and elderly patients. In 2013, skin diseases (not limited to bacterial infections) were the fourth leading cause of disability worldwide (*2*). Cellulitis, the most common skin infection, accounted for 0.04% (4 in 10 000) of the overall burden of all diseases combined in 2013. It was the only skin condition that showed a significant decrease (–13.2%) in disability-adjusted life years (a proxy for morbidity and mortality) between 2005 and 2013; this decrease was attributed to reduced mortality (*2*). In 2017, the Global Burden of Disease study reported 43 million new cases of cellulitis worldwide (*3*). Diabetes, peripheral arterial disease, HIV infection and other causes of immunosuppression are risk factors for severe skin infections.

Summary of evidence: benefits (from the application)

Evidence of the benefits of empiric use of cefalexin for skin and soft tissue infections was reviewed and accepted by the Expert Committee in 2017.

Cefalexin offers good coverage against staphylococcal (non-MRSA) and streptococcal infections with a range of activity and tolerability that is comparable with amoxicillin + clavulanic acid and cloxacillin, the first-choice options currently recommended in the Model Lists for skin and soft tissue infections.

The application proposed that by also including cefalexin as a first-choice option, it will indicate that the three antibiotics are equally adequate options for empiric treatment of mild, community-acquired skin and soft tissue infections. However, it is noted that for skin infections associated with bite wounds, amoxicillin + clavulanic acid remains the preferred treatment option.

Summary of evidence: harms (from the application)

Not applicable

Additional evidence (not in the application)

Not applicable

WHO guidelines

Not applicable

Costs/cost–effectiveness

Not applicable

Availability

Not applicable

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that cefalexin has a spectrum of activity against pathogens responsible for mild to moderate skin and soft tissue infections which is comparable to amoxicillin + clavulanic acid and cloxacillin. The Committee considered that cefalexin as a first-generation cephalosporin is also an appropriate alternative first-choice treatment option for these infections.

The Committee therefore recommended that the listing for cefalexin on the EML and EMLc be amended from a second-choice to a first-choice treatment option for mild to moderate skin and soft tissue infections.

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Cefiderocol – addition – EML

Cefiderocol **ATC Code: J01DI04**

Proposal

Addition of cefiderocol to the complementary list of the EML for the treatment of confirmed or suspected infections due to multidrug-resistant aerobic Gram-negative organisms in adults.

Applicant

Shionogi & Co., Ltd. Osaka, Japan.

WHO technical department

Comments on the application were received from the Department of Global Coordination and Partnership in the Division of Antimicrobial Resistance, which supported the inclusion of cefiderocol on the EML as a Reserve group antibiotic, particularly for use: in hospitalized patients with a confirmed or suspected carbapenem-resistant infection; or when cefiderocol is the best option based on pathogen susceptibility data; or when other treatment choices are inappropriate. The technical department highlighted the need for a mechanism and/or strategy to ensure access to and global affordability of cefiderocol, as well as the need for stewardship.

EML/EMLc

EML

Section

6.2.3 Reserve group antibiotics

Dose form(s) & strength(s)

Powder for injection: 1 g (as sulfate tosylate)

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Cefiderocol has not been previously considered for inclusion on the EML, nor classified under the AWaRe (Access–Watch–Reserve) classification of antibiotics.

Public health relevance (burden of disease)

Antimicrobial resistance is estimated to contribute to 700 000 deaths every year globally (*1*–*3*). If action is not taken, it is estimated that 10 million lives a year will be at risk from drug-resistant infections by 2050 (*1*). The WHO has identified carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant, third-generation cephalosporin-resistant Enterobacteriaceae as critical priority pathogens against which new antibiotics are needed (*4*). Cefiderocol is a parenteral siderophore cephalosporin antibiotic with potent activity against a broad spectrum of Gram-negative pathogens, including these critical priority pathogens.

In its 2018 surveillance report, the European Centre for Disease Prevention and Control reported an increase in resistance to currently available treatments across some Gram-negative pathogens between 2015 and 2018 (*5*). The European Centre estimates that about 700 000 infections and 33 000 deaths in the European Union and European Economic Area in 2015 were caused by from multidrug-resistant bacterial infections (*2*). Carbapenem resistance in *P. aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter* spp. contributed significantly to the number of estimated deaths (in total, about 9000 deaths). In 2015, in five countries (France, Germany, Italy, Spain and United Kingdom), the prevalence of carbapenem-resistant Gram-negative infections ranged between 0.14 per 100 000 in the United Kingdom and 3.05 per 100 000 in Italy (*2*). While carbapenemases appear to vary by geographical location, a recent surveillance study reports an overall increase in these enzymes (*6*, *7*). The prevalence of carbapenem resistance has been particularly high in Mediterranean countries, South America and Asia Pacific countries, except Japan (*6*, *8*).

Summary of evidence: benefits (from the application)

The applicant conducted a comprehensive and systematic literature review for cefiderocol, including in vitro and in vivo studies and any comparative or non-comparative studies and randomized clinical trials.

In vitro studies

The SIDERO-WT analysis investigated the activity of cefiderocol and relevant comparators against carbapenem-susceptible and carbapenem-resistant pathogens (*9*–*11*). To date, 30 459 samples have been tested, with 9205 Gram-negative clinical isolates tested in 2014–2015, 8954 in 2015–2016 and 10 470 in 2016–2017. Cefiderocol was effective at low minimum inhibitory concentrations (MICs) for more than 99% of isolates in each testing period. The latest surveillance SIDERO-WT study (2016–2017) showed that cefiderocol demonstrated activity against 99.4% of Gram-negative pathogens at a MIC of 4 microgram/mL compared with 90.2% for ceftazidime + avibactam, 84.3% for ceftolozane + tazobactam and 95.5% for colistin.

In an analysis of difficult-to-treat resistant pathogens, cefiderocol demonstrated activity against 94.5% of difficult-to-treat resistant *A. baumannii*, 99.8% of *P. aeruginosa* and 98.3% of Enterobacterales; these pathogens were less susceptible to other available treatments. In addition, 98.7% of carbapenem-non-susceptible Enterobacteriaceae, and 96.4% of carbapenem-non-susceptible non-fermenters were sensitive cefiderocol at a MIC of ≤ 4 microgram/mL (*12*).

The SIDERO-CR study collected carbapenem-resistant isolates and multidrug-resistant non-fermenter isolates from Europe, North America, South America and the Asia Pacific region (*9*, *13*). Cefiderocol showed potent in vitro activity against all of these pathogens, as well as activity against isolates with previously characterized resistance factors (*13*).

In vivo studies

APEKS-cUTI was a phase II, multicentre (multinational), double-blind, randomized, active-controlled, parallel-group non-inferiority study conducted in 452 hospitalized adults with complicated urinary tract infections, with or without pyelonephritis or acute uncomplicated pyelonephritis caused by Gram-negative pathogens (*14*). This study assessed the efficacy and safety of intravenous cefiderocol (2 g every 8 hours) compared with intravenous, high-dose imipenem + cilastatin (2 g every 8 hours). The primary efficacy endpoint was the composite of clinical outcome and microbiological outcome at test of cure. The response rate for the primary efficacy endpoint was 73% (183/252) in the cefiderocol group and 55% (65/119) in the comparator group. Cefiderocol met the criteria to demonstrate non-inferiority versus imipenem + cilastatin with a prespecified 20% margin. At follow-up, sustained clinical response was higher in the cefiderocol group than the comparator group (81.3% versus 72.3%), with an adjusted treatment difference of 9.02% (95% confidence interval (CI) –0.37% to 18.41%). The microbiological eradication rate in the modified intention-to-treat population was significantly higher at test of cure in the cefiderocol group than the comparator group (73.0% versus 56.3%). The adjusted treatment difference in favour of cefiderocol (17.25%, 95% CI 6.92% to 27.58%) was statistically significant.

APEKS-NP was a multicentre, double-blind, randomized, phase III clinical study comparing cefiderocol with high-dose, extended-infusion meropenem for the treatment of hospital acquired bacterial pneumonia, ventilator-associated bacterial pneumonia or health care-associated bacterial pneumonia caused by Gram-negative pathogens (*15*). Of the 292 patients in the modified intention-to-treat population, 251 (86%) had a qualifying baseline Gram-negative pathogen, including 92 (32%) with *K. pneumoniae*, 48 (16%) with *P. aeruginosa*, 47 (16%) with *A. baumannii* and 41 (14%) with *Escherichia coli*. The all-cause mortality rate at day 14 was 12.4% for the cefiderocol group and 11.6% for the high-dose meropenem group (treatment difference 0.8%,

95% CI –6.7% to 8.2%, demonstrating the non-inferiority of cefiderocol, as the upper limit of the 95% CI was < 12.5%. For secondary endpoints of clinical cure and microbiological eradication at test of cure, results were similar between treatment groups. Clinical cure rates were 64.8% in the cefiderocol group and 66.7% in the high-dose meropenem group (treatment difference –1.8%, 95% CI –12.7% to 9.0%); microbiological eradication rates were 47.6% for cefiderocol group and 48.0% for high-dose meropenem group (treatment difference –0.8%, 95% CI –12.1% to 10.5%).

The CREDIBLE-CR study was a small, randomized, open-label observational study to evaluate the efficacy of cefiderocol and best available therapy in patients with confirmed carbapenem-resistant infections (nosocomial pneumonia, bloodstream infections or sepsis, or complicated urinary tract infections) (*16*). No formal or inferential analyses were planned for any outcomes to detect differences between the treatment groups. Clinical and microbiological outcomes were similar between treatment groups overall, and by site of infection and causative carbapenem-resistant pathogen.

The quality of the randomized studies was assessed by the applicants. The analysis concluded that the APEKS studies were of high quality with low risk of bias and the CREDIBLE-CR study was of moderate quality.

Case reports of cefiderocol use for compassionate reasons and in expanded access programmes have also reported positive outcomes (*17–25*). A case series of cefiderocol treatment in COVID-19 and burn patients, all ventilated and with carbapenem-resistant infections of *A. baumannii* or other carbapenem-resistant Gram-negative bacteria reported a 90% survival rate after 30 days, with 70% of patients experiencing clinical success (*26*).

Summary of evidence: harms (from the application)

In total, across the APEKS-cUTI, APEKS-NP and CREDIBLE studies, 386 serious adverse events were reported: 226 in patients treated with cefiderocol, 103 in patients treated with meropenem, 17 in patients treated with imipenem + cilastatin and 40 in patients treated with best available therapy.

In the total sample, 56/549 (10.2%) patients treated with cefiderocol experienced treatment-related adverse events and 45/347 (13.0%) patients using comparator treatments experienced treatment-related adverse events. Overall, there were fewer treatment-emergent adverse events with cefiderocol (344/549; 62.7%) than with comparator treatments (252/347; 72.6%). The most common adverse reactions for cefiderocol were diarrhoea (8.2%), constipation (4.6%), pyrexia (4.0%) and urinary tract infection (4.7%).

In total, 22 serious adverse reactions were reported: eight in patients treated with cefiderocol, six in patients treated with meropenem, one in a patient treated with imipenem + cilastatin and seven in patients treated with best available therapy.

The clinical safety for cefiderocol has been investigated in three randomized clinical trials, two specific to different infection sites and one specific to carbapenem-resistant pathogens. In total, 549 patients were treated with cefiderocol in these trails (*14–16*).

In the APEKS-cUTI study, the proportion of patients who experienced at least one adverse event was lower in the cefiderocol group than in the imipenem + cilastatin group (41% versus 51%). The most common adverse events were diarrhoea (4% versus 6%), hypertension (4% versus 5%) and constipation (3% versus 4%), and there was an increased incidence of *C. difficile* colitis in the imipenem + cilastatin group compared with the cefiderocol group. Serious adverse events occurred in a smaller proportion of patients treated with cefiderocol than patients treated with imipenem + cilastatin (5% versus 8%) (*14*).

In the APEX-NP study, overall, treatment-emergent adverse events and treatment-related adverse events were similar between treatment arms. Serious adverse events occurred in 36% of patients using cefiderocol and 30% of patients using meropenem. The most frequently observed adverse event was urinary tract infection (15.5% in the cefiderocol group and 10.7% in the meropenem group), hypokalaemia (10.8% cefiderocol group and 15.3% meropenem group) and anaemia (8.1% cefiderocol group and 8% meropenem group) (*15*).

In the CREDIBLE-CR study, the cefiderocol group had a lower incidence of adverse events and treatment-related adverse events, but a higher incidence of death, serious adverse events and discontinuation due to adverse events, compared with the best available treatment group (*16*). The incidence of treatment-related adverse events leading to discontinuation was similar between treatment groups. More deaths occurred in the cefiderocol group than the best available treatment group. In an assessment by the investigator and two independent committees (one blinded), no deaths were found to be causally associated with cefiderocol. The mortality rate in the cefiderocol group was consistent with previous studies in similar populations with high levels of *A. baumannii* infections (*27–29*). However, the mortality rate in the best available treatment group was substantially lower than expected from previous studies (*27–35*). The reason for this lower than expected mortality is not clear. Still, it may be influenced by various factors related to baseline imbalances and other anomalies (such as the low mortality associated with high APACHE II and SOFA scores).

Cefiderocol has demonstrated a manageable safety profile with the longest use being more than 90 days in a renal transplant patient where no apparent safety issues were observed (*34*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

Cefiderocol is a newly approved antimicrobial so is not yet included in many formal clinical guidelines. However, its usefulness against several multidrug resistant pathogens has been recognized by both WHO and the Infectious Diseases Society of America (*36*, *37*).

In the 2019 WHO report on antibacterial agents in clinical development, cefiderocol was identified as a siderophore cephalosporin that is active against many WHO priority pathogens, including extended spectrum beta-lactamase-producing Enterobacterales, *K. pneumoniae* carbapenemase and oxacillinase-48-producing Enterobacterales (*36*).

Costs/cost–effectiveness

Cefiderocol is appropriate for treating infections caused by aerobic Gram-negative organisms in adults who have limited treatment options. Treatment options may be limited because of multidrug-resistant or carbapenem-resistant pathogens, which are associated with higher mortality rates and increased clinical and economic burden.

Without definitive evidence that an infection is resistant to first-line treatment, empiric therapy may be used, and appropriate treatment may be delayed. A recent systematic review examined the effect of delayed antibiotic therapy in patients with severe bacterial infections. It concluded that mortality was significantly lower in patients who did not experience a delay in receiving the appropriate therapy (*38*). Several systematic reviews have examined the effect of antimicrobial resistance and multidrug-resistant infections on health care costs, and all found an association between increased costs and resistance (*39*–*41*). As a result, antibiotics that can effectively treat multidrug-resistant infections can potentially provide health benefits and health care savings.

The wholesale acquisition of cefiderocol (10 vials) in the United Kingdom and the USA was reported in the application as £ 1319.00 and US$ 1833.33, respectively. Length of treatment varies from patient to patient, depending on infection site and underlying patient conditions. The dose of cefiderocol varies with renal function, but for a normal renal function, the standard dose is 2 g by infusion every 8 hours. This represents a daily dose of six vials a day, at a cost of £ 791.40 a day in the United Kingdom and US$ 1100 a day in the USA.

A cost–effectiveness analysis compared cefiderocol with colistin-based regimens to treat complicated urinary tract infections and hospital-acquired and ventilator-associated pneumonia caused by confirmed carbapenem-resistant pathogens (*42*). It concluded that cefiderocol was a cost-effective option compared with the colistin-based treatment, with an incremental cost–effectiveness ratio of US$ 14 616 per quality-adjusted life year.

Availability

Cefiderocol is manufactured by Shionogi & Co. Ltd (Japan) and has regulatory approval from the US Food and Drug Administration and the European Medicines Agency. It is currently available in Germany, United Kingdom and USA. Reimbursement and health-technology assessments are in process in other European countries.

Other considerations

Not applicable

Committee Recommendations

The Expert Committee noted that antimicrobial resistance is a global public health threat and that effective antibiotics against multidrug-resistant Gram-negative organisms, such as carbapenem-resistant Enterobacterales (a critical priority pathogen on WHO's priority pathogens list), are urgently needed.

The Committee further noted that very few options are currently available to treat Gram-negative organisms that produce metallo-beta-lactamases, which are highly endemic in some WHO regions. Cefiderocol offers activity against some of the critical and high-priority multidrug-resistant, Gram-negative pathogens, including those producing metallo-beta-lactamases, against which other antibiotics listed on the EML have no or only limited activity. The Committee also accepted that cefiderocol has a safety profile consistent with other beta-lactams.

The Expert Committee noted that the two double-blinded studies (APEKS-cUTI and APEKS-NP) on which regulatory authority approval of cefiderocol is based applied a non-inferiority design, a common practice in antibiotic trials. Both trials demonstrated that cefiderocol was non-inferior to carbapenems with regard to microbiological and clinical response and mortality, despite large non-inferiority margins being applied. Of note, the presence of an infection caused by multidrug-resistant organisms was not an inclusion criterion in these trials. In addition, the pathogen-focused phase III CREDIBLE-CR trial comparing cefiderocol with best available therapy showed similar clinical cure for treatment of infections caused by carbapenem-resistant Gram-negative bacteria. However, there was a higher mortality at the end of the study in the subset of patients infected with *Acinetobacter* spp.

The Committee therefore recommended the inclusion of cefiderocol in the complementary list of the EML as a Reserve group antibiotic, based on an acceptable benefit-to-risk profile and high public health need. The increased mortality observed in the CREDIBLE-CR study was a major concern and deserves further, careful study. Therefore, the Expert Committee did not recommend cefiderocol for treatment of proven *Acinetobacter* spp. infections at this time.

Given the nature of cefiderocol as a last-resort Reserve antibiotic, the Committee stressed that special attention should be given to antibiotic stewardship measures to avoid inappropriate use. Strategies and policies to ensure access to this high-cost antibiotic in low-resource settings also need to be defined.

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Antibiotics – new formulations – EML

Antibiotics – new strength formulations — ATC Code: various

Proposal

Inclusion of new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults.

Applicant

Mark Loeb, Dominik Mertz; McMaster University, Hamilton, Canada
Veronica Zanichelli; WHO consultant

WHO technical department

Global Coordination and Partnership (Division of Antimicrobial Resistance)
Surveillance, Prevention and Control (Division of Antimicrobial Resistance)

EML/EMLc

EML

Section

6.2.1 Access group antibiotics
6.2.2 Watch group antibiotics

Dose form(s) & strength(s)

Amoxicillin: solid oral dosage form 1 g
Cefalexin: solid oral dosage form 500 mg
Ceftriaxone: powder for injection 2 g
Ciprofloxacin: solid oral dosage form 500 mg
Clindamycin: injection 600 mg/4 mL, 900 mg/6 mL
Phenoxymethylpenicillin: tablet 500 mg
Vancomycin: powder for injection 500 mg, 1 g

Core/complementary

Complementary (vancomycin), core (all others)

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

All of the antibiotics for which additional strength formulations are proposed are currently included on the EML is various other formulations and strengths for the indications described below (*1*).

Public health relevance (burden of disease)

The proposed new formulations are higher strength dosage forms than those currently listed on the EML, and are aligned to meet the dosing needs of adults. The proposed higher strength formulations should enable prescribers to more effectively treat common bacterial infections.

Summary of evidence: benefits (from the application)

Amoxicillin: solid oral dosage form 1 g

Most adult and adolescent patients with mild community-acquired pneumonia or acute bacterial sinusitis can be successfully treated with amoxicillin 1 g every 8 hours for 5 days. The proposed 1 g oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 500 mg strength formulation, and should facilitate adherence to treatment.

Cefalexin: solid oral dosage form 500 mg

Most adult patients diagnosed with exacerbations of chronic obstructive pulmonary disease, can be successfully treated with cefalexin 500 mg every 12 hours for 5 days. For bacterial pharyngitis and mild skin and soft tissue infections, most adult and adolescent patients can be successfully treated with cefalexin 500 mg every 8 hours for 5 days. The proposed 500 mg oral formulation will allow for a reduced pill burden to complete a course of treatment compared with the currently listed 250 mg strength formulation, and should facilitate adherence to treatment.

Ceftriaxone: powder for injection 2 g

This higher strength formulation is preferable for the treatment of certain infections because it maximizes the chances of bacterial eradication in order to achieve clinical success. For example, in the case of acute bacterial meningitis, a ceftriaxone dose of 2 g every 12 hours is needed to achieve adequate concentrations of the drug in the central nervous system. The recommended duration of treatment is 10 days. For adult patients with hospital-acquired pneumonia and no risk factors for multidrug-resistant infections, ceftriaxone 2 g a day for 7 days is a recommended treatment regimen. For complicated intra-abdominal infections, ceftriaxone 2 g per day for 5 days (in combination with metronidazole) is a recommended treatment in cases where extended-spectrum

beta-lactamase strains are not suspected. For severe cases of enteric fever, if ceftriaxone is used, a dose of 2 g per day for 10 days is recommended.

Ciprofloxacin: solid oral dosage form 500 mg

The proposed higher strength formulation will benefit adult and adolescent patients prescribed ciprofloxacin for infections including acute invasive bacterial diarrhoea, cholera, complicated intra-abdominal infections, enteric fever, low-risk febrile neutropenia and upper urinary tract infections. Treatment regimens recommend ciprofloxacin doses of 500 mg every 12 hours for 3, 5 or 7 days, depending on the indication or, in the case of cholera, a single dose of 1 g. The proposed 500 mg oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 250 mg strength formulation, and should facilitate adherence to treatment.

Clindamycin: injection 600 mg/4 mL, 900 mg/6 mL

The higher strength formulations of clindamycin are preferable for the treatment of bone and joint infections to maximize the chance of bacterial eradication in order to achieve clinical success. For adults and adolescents diagnosed with osteomyelitis, clindamycin is an acceptable treatment option when methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or confirmed when antimicrobial susceptibility of MRSA to clindamycin is proven or likely. Intravenous clindamycin at a dose of 600 mg every 8 hours for 4–6 weeks is a recommended dosage regimen in most cases. Clindamycin may also be used in patients allergic to penicillin.

Phenoxymethylpenicillin: solid oral dosage form 500 mg

Most adult and adolescent patients with mild community-acquired pneumonia, bacterial pharyngitis or dental infections can be successfully treated with phenoxymethylpenicillin 500 mg every 6 hours for 5 days; however, a longer treatment duration may be recommended in some circumstances. The proposed 500 mg strength oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 250 mg strength formulation and should facilitate adherence to treatment.

Vancomycin: powder for injection 500 mg, 1 g

For adult and adolescent patients with high-risk febrile neutropenia when MRSA infection is suspected, weight-based dosing of vancomycin is recommended (15–20 mg/kg every 12 hours). The 500 mg and 1 g strength formulations will allow for the achievement of recommended dose using fewer vials, compared with the currently listed 250 mg strength.

Summary of evidence: harms (from the application)

Not applicable

Additional evidence (not in the application)

Not applicable

WHO guidelines

Not applicable

Costs/cost–effectiveness

No information provided

Availability

All proposed formulations are approved by several regulatory agencies including the US Food and Drug Administration and European Medicines Agency, and are available in most countries.

Other considerations

Not applicable

Committee recommendations

The Expert Committee recommended the addition of the new strength formulations of amoxicillin, cefalexin, ceftriaxone, ciprofloxacin, clindamycin, phenoxymethylpenicillin and vancomycin to the existing listings of these medicines on the EML for the indications for which they are proposed.

The Committee noted that the proposed strength formulations are higher than those currently included on the Model List, and are appropriate and aligned to meet recommended doses for treatment of adults, with the advantages of a reduced pill burden in the case of oral formulations, and facilitating a simplified and safer dose administration in the case of intravenous formulations.

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6.2.5 Antituberculosis medicines

Moxifloxacin and rifapentine – new indication – EML

Moxifloxacin	**ATC Code: J01MA14**
Rifapentine	**ATC Code: J04AB05**

Proposal

Extension of the indications for moxifloxacin and rifapentine on the EML to include a new indication for treatment of drug-susceptible tuberculosis in adults and children over 12 years of age.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Moxifloxacin: tablet 400 mg
Rifapentine: tablet 150 mg, 300 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Moxifloxacin 400 mg tablets were added to the complementary list of the EML and EMLc in 2017 for use in the treatment of multidrug-resistant tuberculosis (*1*). In 2019, a 100 mg dispersible tablet formulation was added to the complementary list of the EMLc for this indication for use in children (*2*).

Rifapentine (150 mg tablet) was added to the core list of the EML and EMLc in 2015 for treatment, in combination with isoniazid, of latent tuberculosis infection (now known as tuberculosis preventive treatment) (*3*). A separate

application to the 2021 Expert Committee meeting requests listing for a 300 mg strength tablet of rifapentine for tuberculosis preventive treatment.

Public health relevance (burden of disease)

The public health relevance of medicines for the treatment of tuberculosis is well established. Globally in 2019, an estimated 10 million people fell ill with tuberculosis, 1.2 million deaths occurred among HIV-negative people and 208 000 deaths among HIV-positive people (*4*).

Treatment of drug-susceptible pulmonary tuberculosis is a standard 6-month daily regimen, composed of 2 months of isoniazid (H), rifampin (R), ethambutol (E) and pyrazinamide (Z) followed by 4 months of isoniazid and rifampin (2HREZ/4HR). The standard 6-month regimen is well known and widely implemented worldwide. Rifapentine-based regimens have potent antimycobacterial activity and may allow shortening of a treatment course in patients with drug-susceptible pulmonary tuberculosis.

Summary of evidence: benefits (from the application)

The Tuberculosis Trials Consortium Study 31/AIDS Clinical Trials Group A5349 (Study 31/A5349) was an international, multicentre, randomized, open-label, phase III, non-inferiority trial that aimed to determine whether treatment regimens that included rifapentine, at a once-daily dose of 1200 mg (with or without a once-daily dose of 400 mg of moxifloxacin) can provide a durable cure in participants with drug-susceptible pulmonary tuberculosis in 4 months, as compared with the standard 6-month regimen (*5*).

Two shorter regimens were assessed: (i) 2 months of isoniazid (H), rifapentine (P), ethambutol (E) and pyrazinamide (Z), followed by 2 months of isoniazid and rifapentine (2PHZE/2PH), with rifapentine replacing rifampin; and (ii) 2 months of isoniazid, rifapentine, moxifloxacin (M) and pyrazinamide, followed by 2 months of isoniazid, rifapentine and moxifloxacin (2PHZM/2PHM), with rifapentine replacing rifampin and moxifloxacin replacing ethambutol. These two 4-month regimens were compared with a standard 2RHZE/4RH regimen using a non-inferiority margin of 6.6 percentage points. The primary efficacy outcome was survival free of tuberculosis at 12 months after randomization, and safety was assessed through day 14 after the last dose of a trial drug.

The rifapentine with moxifloxacin regimen was non-inferior to the control regimen in the microbiologically eligible population (15.5% versus 14.6% had an unfavorable outcome; difference 1.0 percentage point, 95% confidence interval (CI) −2.6 to 4.5) and in the assessable population (11.6% versus 9.6%; difference 2.0 percentage points; 95% CI −1.1 to 5.1). Non-inferiority was shown in the secondary and sensitivity analyses.

Non-inferiority of the rifapentine without moxifloxacin regimen to the control regimen was not shown in either the microbiologically eligible population (17.7% versus 14.6% with an unfavorable outcome; difference 3.0 percentage points, 95% CI −0.6 to 6.6) or the assessable population (14.2% versus 9.6%; difference 4.4 percentage points, 95% CI 1.2 to 7.7).

Summary of evidence: harms (from the application)

No evidence of a difference between the rifapentine with moxifloxacin and control regimens in the primary safety outcome was found: on-treatment grade 3 or higher adverse events were reported in 159 (18.8%) participants in the rifapentine–moxifloxacin regimen and 159 (19.3%) in the control regimen (adjusted difference −0.6, 95% CI −4.3 to 3.2). The percentage of participants with on-treatment grade 3 or higher adverse events was lower in the rifapentine without moxifloxacin regimen than the control regimen (adjusted difference −5.1, 95% CI −8.7 to −1.5). In addition, all-cause mortality during treatment was low and similar across treatment regimens (0.8%, 0.4% and 0.5% in the control, rifapentine–moxifloxacin and rifapentine regimens, respectively) (*5*).

There was no evidence of a difference in tolerability between the rifapentine–moxifloxacin regimen and the control regimen (risk difference −1.0, 95% CI −3.6 to 1.6). The rifapentine regimen was better tolerated than the control regimen (−3.3, 95% CI −5.7 to −0.9) (*5*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

The WHO Global Tuberculosis Programme received data from the Study 31 investigators and convened a guideline development group in April 2021 to review study results.

The available evidence reviewed by the guideline development group on the 4-month regimen for treatment of drug-susceptible pulmonary tuberculosis supports the use of this regimen as a possible alternative to the current standard 6-month regimen. The shorter regimen has showed similar performance to the current standard regimen, both in terms of efficacy and safety. The 4-month regimen, which is shorter, effective and all oral, would be preferred by many patients and also national tuberculosis programmes, allowing faster cure and easing the burden on both patients and the health care system. However, implementation and uptake of the new regimen in the short to medium term will be more feasible if the cost of rifapentine is reduced and its availability improved. Rigorous antibacterial stewardship will also be required to ensure the appropriate use of the first-line regimen given that it contains moxifloxacin, an antibiotic usually used for the treatment of drug-resistant tuberculosis.

Updated WHO policy guidelines will be released later in 2021, as part of the 2021 update of the WHO consolidated guidelines on tuberculosis. The guidelines will incorporate all current recommendations on the treatment of drug-susceptible tuberculosis (*6*).

Costs/cost–effectiveness

Cost–effectiveness data were not presented in the application. The guideline development group noted that implementation and uptake of the new regimen in the short to medium term will be more feasible if the cost of rifapentine is reduced and its availability improved.

Availability

Not applicable

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with *Mycobacterium tuberculosis*, with the life-time risk of developing tuberculosis disease of about 5–10% among those infected.

The Committee noted the results from Study 31 that a shorter 4-month regimen containing isoniazid, moxifloxacin, rifapentine and pyrazinamide was shown to be non-inferior to the standard 6-month regimen containing ethambutol, isoniazid, pyrazinamide and rifampin for patients with drug-susceptible tuberculosis. The Committee also noted that the 4-month regimen containing moxifloxacin and rifapentine will be included in the updated WHO guidelines for treatment of drug-susceptible tuberculosis. The Committee considered that a reduction in the length of the course of treatment from 6 months to 4 months may improve patient adherence and result in cost savings.

The Expert Committee therefore recommended the inclusion of moxifloxacin 400 mg tablets and rifapentine 150 mg and 300 mg tablets on the core list of the EML for the new indication of treatment of drug-susceptible tuberculosis in adults and children older than 12 years of age.

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Pyrazinamide – new formulation – EML and EMLc

Pyrazinamide	**ATC Code: J04AK01**

Proposal

Inclusion of a new strength formulation (500 mg tablet) of pyrazinamide for the treatment of tuberculosis.

Applicant

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Brian Kaiser; Stop TB Partnership/Global Drug Facility

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Tablet: 500 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Pyrazinamide 500 mg tablets were added to the EML in 1982 for the treatment of tuberculosis. In 1995, the 500 mg strength tablet was replaced by a 400 mg strength tablet, which remains listed currently. The current EML also includes 150 mg strength tablet formulations.

Pyrazinamide is also included in the EML as part as single-pill combinations with ethambutol, isoniazid and rifampicin. The strength of pyrazinamide in these combination formulations is 400 mg.

Public health relevance (burden of disease)

Globally, an estimated 10 million people fell ill with tuberculosis in 2019, a number that has been declining slowly in recent years. An estimated 1.2 million deaths caused by tuberculosis occurred among HIV-negative people in 2019 and an additional 208 000 deaths among HIV-positive people. Men (aged ≥ 15 years) accounted for 56% of the people who developed tuberculosis in 2019, women accounted for 32% and children (aged < 15 years) for 12%. Of all those affected by tuberculosis, 8.2% were people living with HIV. Drug-resistant tuberculosis continues to be a public health threat. In 2019, about half a million people developed rifampicin-resistant tuberculosis, of whom 78% had multidrug-resistant tuberculosis (*1*).

About 85% of people who develop drug-susceptible tuberculosis and 57% who develop multidrug-resistant tuberculosis can be successfully treated with a 6-month drug regimen (*1*).

Summary of evidence: benefits (from the application)

The application highlighted that the proposed 500 mg strength formulation may lead to better adherence to treatment as a result of a reduced pill burden. WHO recommends a dose of 30–35 mg/kg a day for pyrazinamide. Recommended weight-band dosing for pyrazinamide with 400 mg and 500 mg strength tablets is shown below, highlighting the lower pill burden for patients weighing more than 30 kg with the 500 mg strength formulation. A higher pill burden has been associated with lower rates of treatment adherence, which could lead to poor treatment outcomes, increased morbidity and mortality, the development of drug resistance and ongoing transmission of tuberculosis (*2*).

Weight band (kg)	WHO-recommended dose (mg/day)	Number of 400 mg tablets	Number of 500 mg tablets
30–35	1000–1200	3	2
36–45	1500–1600	4	3
46–55	1500–1600	4	3
56–70	1500–1600	4	3
> 70	2000	5	4

Summary of evidence: harms (from the application)

Pyrazinamide has been used in the treatment of tuberculosis for more than 50 years and its safety profile is well known.

The pharmacokinetics and pharmacodynamics of pyrazinamide have been confirmed in many studies involving different formulations including the 400 mg and 500 mg tablets (*3*–*7*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

Regimens including pyrazinamide are recommended by WHO guidelines for treatment of both drug-susceptible and drug-resistant tuberculosis (*8*–*10*).

Costs/cost–effectiveness

Pyrazinamide 500 mg tablets are available from the Stop TB Partnership Global Drug Facility at a price of US$ 13.40–14.00 per pack. In contrast, the price for the 400 mg tablets is US$ 14.00 per pack. In both cases the pack size is 672 tablets.

Availability

There are three suppliers of pyrazinamide 500 mg tablets that are currently prequalified by the WHO Prequalification of Medicines Programme: Micro Labs, Macleods Pharmaceuticals Ltd and Antibiotice SA. Additional quality-assured suppliers are approved by the US Food and Drug Administration.

According to unpublished data from the Global Drug Facility, the procurement of pyrazinamide 400 mg and 500 mg tablets was about equal between 2014 and 2017. In 2018, however, procurement of the 500 mg tablet was more than 80% of all single formulations of pyrazinamide and was more than 60% in 2019 and 2020, indicating that this formulation is already being procured and used, despite not being on the EML.

Other considerations

Not applicable

Committee Recommendations

The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with *Mycobacterium tuberculosis*, with the life-time risk of developing tuberculosis of about 5–10% among those infected.

The Expert Committee noted pyrazinamide 400 mg tablet is already listed in the EML and the addition of 500 mg formulation would help reduce the pill burden for patients and may increase adherence to treatment. It also noted that pyrazinamide 500 mg is already listed in many national essential medicine lists.

Therefore, the Expert Committee recommended the inclusion of the pyrazinamide 500 mg tablet formulation in the core list of the EML and EMLc for the treatment of tuberculosis.

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Rifapentine – new formulation – EML and EMLc

Rifapentine **ATC Code: J04AB05**

Proposal

Inclusion of a new strength formulation (300 mg) of rifapentine tablets for tuberculosis preventive treatment (previously known as treatment of latent tuberculosis infection).

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Tablet (scored): 300 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Rifapentine (150 mg tablet) was added to the core list of the EML and EMLc in 2015 for treatment, in combination with isoniazid, of latent tuberculosis infection (now known as tuberculosis preventive treatment) (*1*).

The 2015 application presented a network meta-analysis of treatments for latent tuberculosis infection for preventing the development of active disease in individuals identified at high risk of progression (*2*). Fifty-three randomized controlled trials evaluated treatment for latent tuberculosis infection and recorded at least one of the two prespecified endpoints (prevention of active tuberculosis and/or hepatotoxicity of grade III or above). The results of clinical trials demonstrated the effectiveness of the 12-week regimen of rifapentine

and isoniazid (3HP), administered once weekly for the treatment of latent tuberculosis infection in adults compared with the 6- or 9-month isoniazid regimen, considered as standard for this indication. Randomized controlled trials explored the effectiveness of rifapentine in combination with isoniazid for children aged 2 years and older (*3*), people with HIV-infection (*4*) and people without HIV infection (*3*). The rifapentine plus isoniazid combination was non-inferior in terms of efficacy, and had significantly better treatment adherence and completion of the 12-week regimen compared with isoniazid alone.

Universal treatment of all individuals with latent tuberculosis infection is not recommended because of uncertainties about the balance between benefit and harm. A positive benefit–harm trade-off is evident in individuals with latent tuberculosis infection who are at risk for progression to active tuberculosis disease, that is: people living with HIV; adult and child contacts of pulmonary tuberculosis cases; patients starting treatment with an antitumour necrosis factor; patients receiving dialysis; patients preparing for organ or haematological transplantation; and patients with silicosis (*5*, *6*).

In terms of harms, the 12-week rifapentine plus isoniazid regimen was shown to be well tolerated when used for the treatment of latent tuberculosis infection, including in children and in adults with and without HIV infection (*2*, *3*). The 12-week combination regimen was associated with less hepatotoxicity and more possible hypersensitivity reactions than the standard 6- or 9-month isoniazid therapy. In total, five deaths attributable to toxicity were reported, mostly from a single trial. All deaths were due to severe hepatitis in isoniazid treatment groups, and at least four occurred in patients who were on isoniazid for 12 months or longer (*2*). In the TBTC-S26 main study, the overall incidence of serious adverse events was low; serious adverse events were reported in 2.7% of patients in the isoniazid arm and 1.5% of patients in the rifapentine plus isoniazid arm (*3*). In the paediatric substudy of TBTC-S26, serious adverse events were reported in six children (1.2%), all of whom were in the isoniazid arm. In the HIV substudy of TBTC-S26, serious adverse events were reported in 10.8% of patients receiving isoniazid and 3.9% of patients receiving rifapentine plus isoniazid.

Public health relevance (burden of disease)

Globally, an estimated 10 million people fell ill with tuberculosis in 2019, a number that has been declining slowly in recent years. An estimated 1.2 million deaths caused by tuberculosis occurred among HIV-negative people in 2019, and an additional 208 000 deaths among HIV-positive people. Men (aged ≥ 15 years) accounted for 56% of the people who developed tuberculosis in 2019, women accounted for 32% and children (aged < 15 years) for 12%. Of all those affected by tuberculosis, 8.2% were people living with HIV (*7*).

About a quarter of the world's population is infected with *Mycobacterium tuberculosis*, with the life-time risk of developing tuberculosis disease of about 5–10% among those infected (*8*). Preventive treatment is available for people with tuberculosis infection. Prevention of new infections of *M. tuberculosis* and their progression to tuberculosis disease is critical to reduce the burden of ill health and death caused by tuberculosis, and to achieve the End TB Strategy targets set for 2030 and 2035. Current health interventions for tuberculosis prevention, in addition to tuberculosis preventive treatment, include the prevention of transmission of *M. tuberculosis* through infection prevention and control, and vaccination of children with the bacille Calmette–Guérin (BCG) vaccine.

Tuberculosis preventive treatment reduces the risk of progression from tuberculosis infection to tuberculosis disease by about 60% but this reduction can be as high as 90% among certain high-risk groups, such as people living with HIV (*9*, *10*). Systematic tuberculosis preventive treatment is currently recommended by WHO for: household contacts of bacteriologically confirmed pulmonary tuberculosis patients, people living with HIV, people with silicosis, people receiving dialysis or antitumour necrosis factor treatment, and people preparing for haematological or organ transplantation. Depending upon the country context, people with risk factors other than those mentioned above (such as prisoners, non-household close contacts and people with diabetes) can also be considered for systematic screening and tuberculosis preventive treatment. At the first UN high-level meeting on tuberculosis in 2018, Member States committed to providing tuberculosis preventive treatment to at least 30 million people in the 5-year period 2018–2022, including 6 million people living with HIV, 4 million children aged under 5 years who are household contacts of people with bacteriologically confirmed tuberculosis, and 20 million household contacts in older age groups.

Summary of evidence: benefits (from the application)

Evidence for the benefits of rifapentine was reviewed in 2015 (see Background section).

The effectiveness of the 300 mg formulation is not expected to differ from the 150 mg formulation, as long as the tablet is a quality-assured product with proven bioavailability.

In general, providing tuberculosis preventive treatment to high-risk individuals prevents morbidity and mortality at the individual level and reduces the tuberculosis burden by limiting its transmission from individuals who would otherwise develop tuberculosis. Recent epidemiological data from the WHO South-East Asia region indicate that tuberculosis disease prevention at scale is an essential intervention if the End TB Strategy targets are to be met. Optimal implementation of tuberculosis preventive treatment alone in certain high-risk

groups, such as household contacts or people living with HIV, has the potential to reduce the annual tuberculosis incidence rate by 8.3% (95% credible interval (CrI) 6.5 to 10.8) relative to 2015, in the absence of any additional interventions (*11*, *12*).

Summary of evidence: harms (from the application)

Evidence for the harms of rifapentine was reviewed in 2015 (see Background section).

The harms associated with the 300 mg formulation are not expected to differ from the 150 mg formulation as long as the tablet is a quality-assured product with proven bioavailability.

Nitrosamine impurities in rifapentine have recently stopped its production and distribution (*13*, *14*). The WHO Prequalification Unit reported on 30 October 2020 that it was in contact with Sanofi about the presence of 1-cyclopentyl-4-nitrosopiperazine in the Priftin brand of rifapentine, a medicine that had prequalified based on approval of the US Food and Drug Administration. As per its notification of 29 October 2020, the US Food and Drug Administration will not object to the temporary distribution of rifapentine containing 1-cyclopentyl-4-nitrosopiperazine below 20 parts per million. The WHO Prequalification Unit recognizes the decision of the US Food and Drug Administration for this product.

Additional evidence (not in the application)

Not applicable

WHO guidelines

Regimens including rifapentine for tuberculosis preventive treatment are recommended by WHO in the 2020 WHO consolidated guidelines on tuberculosis (*15*, *16*).

The following options are recommended regardless of HIV status.

- 6 or 9 months of daily isoniazid, or
- a 3-month regimen of weekly rifapentine plus isoniazid, or
- a 3-month regimen of daily isoniazid plus rifampicin, or
- a 1-month regimen of daily rifapentine plus isoniazid, or
- a 4-month regimen of daily rifampicin.

The recommended dose of rifapentine in rifapentine-containing tuberculosis preventive treatment regimens is:

- 1200 mg per week for patients aged > 14 years (for the 3-month regimen of rifapentine plus isoniazid)

- 600 mg per day for patients aged ≥ 13 years (for the 1-month regimen of daily rifapentine plus isoniazid).

The 300 mg strength formulation would reduce the pill burden for patients.

Costs/cost–effectiveness

The median cost per person treated for drug-susceptible tuberculosis in 2019 was US$ 860 and about US$ 5660 for treatment of multidrug-resistant tuberculosis (*7*). Recent modelling work in the WHO South-East Asia region showed that the number of individuals at high risk of tuberculosis disease who need preventive treatment to avert one tuberculosis case is 64 (95% CrI 55 to 74), which is considered an attractive public health proposition (*12*). Tuberculosis preventive treatment can result in important savings for the individual and the health system by avoiding the need for tuberculosis treatment, given the longer isoniazid monotherapy regimens needed for treatment of tuberculosis disease. Further reductions in the cost of rifapentine will make this tuberculosis preventive treatment even more advantageous. The standard regimen of 6 months isoniazid monotherapy has been the most widely used tuberculosis preventive treatment option, costing US$ 4–6 for a patient course. However, the uptake and completion of tuberculosis preventive treatment with this longer regimen has been limited (*17*).

Furthermore, WHO considers the 3-month regimen of weekly rifapentine + isoniazid and the 1-month regimen of daily rifapentine + isoniazid as equivalent options for tuberculosis preventive treatment among high-risk individuals across all epidemic settings. Individuals on shorter regimens were shown to be 1.5–3 times more likely to complete treatment, which is important to maximize its effectiveness in preventing active tuberculosis (*18–21*). In published literature, the cost–effectiveness of the two rifapentine-containing regimens has primarily been studied in high-income, low-burden settings using the price of Sanofi-branded rifapentine (Priftin). In high-burden, low-resource settings, researchers have found the 3-month regimen of weekly rifapentine + isoniazid with directly observed therapy prevents the greatest number of tuberculosis cases compared with other regimens for latent tuberculosis infection, but at a cost of US$ 9402 per disability-adjusted life year (DALY) averted (*22*). If the price of rifapentine were reduced to US$ 8, the researchers estimated the incremental cost–effectiveness ratio would decrease to US$ 535 per DALY averted. Hence, although currently more costly compared to the isoniazid-only regimen, tuberculosis preventive treatment containing rifapentine is expected to be more cost-effective option for tuberculosis programmes.

Rifapentine, although off patent, is currently only available from Sanofi, the innovator. There are no other quality-assured sources. In high-income countries, Sanofi sells the drug as a 150 mg tablet at US$ 1 per tablet or US$ 73 for a full patient course of the 3-month regimen inclusive of isoniazid. Through the Global Drug Facility, the company sells the drug for US$ 0.625 per tablet or US$ 46 per treatment course. This cost is significantly higher than the US$ 4–6 for the 6-month isoniazid regimen. Sanofi has entered into an agreement with the Global Fund to Fight AIDS, Tuberculosis and Malaria and Unitaid to reduce the price of rifapentine to US$ 15 per adult patient course for a select set of countries with a high burden of tuberculosis.

Additional suppliers of a more suitable formulation will increase supply security and competition, leading to lower prices without the geographic limitations.

Availability

Two suppliers are developing a rifapentine 300 mg formulation. One supplier has successfully completed stability and pilot bioequivalence studies on the prototype product. Once 6 months of stability information is available, the product will be submitted for review by the WHO Prequalification Programme and the Global Fund's Expert Review Panel. A second supplier of the 300 mg formulation is on a similar timeline. As soon as the WHO Prequalification Programme has accepted the product dossiers for review, the products can be reviewed by the Global Fund's Expert Review Panel. The Expert Review Panel makes recommendations to the Global Fund to allow procurement while a product is undergoing quality assurance review by WHO. Rifapentine 300 mg is a priority product for review by the Expert Review Panel, meaning the recommendation could be made in only 6 weeks from the time of dossier submission. Thus, availability of this product on the market would be expected in late 2021. These new products should help alleviate some of the backlog of demand for rifapentine-based short-course tuberculosis preventative treatment. As there is currently only one supplier of a non-ideal formulation of rifapentine, a Rifapentine Consortium composed of some of the main technical and funding partners that support WHO's drive to scale-up tuberculosis preventive treatment globally was established in 2019. The function of the Consortium is to allocate the very limited available supply against the increasing programmatic demand. Having additional suppliers of a more suitable formulation should help restore the normal market dynamics for rifapentine and the Rifapentine Consortium will no longer be required.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with *M. tuberculosis*, with the life-time risk of developing active disease of about 5–10% among people infected.

The Committee considered that tuberculosis preventive treatment reduces the risk of progression from tuberculosis infection to tuberculosis disease by about 60% but this reduction can be as high as 90% among certain high-risk groups. Systematic tuberculosis preventive treatment is currently recommended by WHO for target populations at high risk. Furthermore, with the commitments from governments and donors, the availability of shorter regimens is expected to facilitate uptake of tuberculosis preventive treatment.

The Committee noted that rifapentine 150 mg has been on the core list of the EML for tuberculosis since 2015, as part of the preferred shorter tuberculosis preventive treatment regimens of rifapentine in combination with isoniazid as a weekly dose for 3 months (3HP) or a daily regimen for 1 month (1HP). The 300 mg formulation of rifapentine would reduce the pill burden by half, thus significantly improving the likelihood of treatment adherence. In addition, individuals on shorter regimens have been shown to be 1.5–3 times more likely to complete the treatment course, which is a significant determinant of the regimen's effectiveness in preventing active tuberculosis.

The Committee considered that the overall benefit to risk ratio of the rifapentine 300 mg formulation greatly favours its use for the shorter tuberculosis preventive treatment regimens. Availability of rifapentine 300 mg on the market is expected in late 2021. Additional suppliers of this formulation will increase supply security and competition, leading to lower prices and affordability.

The Expert Committee therefore recommended the inclusion of the rifapentine 300 mg scored tablet formulation for the indication of tuberculosis preventive treatment on the core list of the EML and EMLc.

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Rifapentine + isoniazid – new formulation – EML and EMLc

Rifapentine + isoniazid **ATC Code: J04AC51**

Proposal

Inclusion of a single-pill combination formulation of rifapentine plus isoniazid for tuberculosis preventive treatment (previously known as treatment of latent tuberculosis infection).

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Tablet (scored): 300 mg + 300 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Single ingredient formulations of rifapentine and isoniazid are currently included on the EML.

Public health relevance (burden of disease)

Globally, an estimated 10 million people fell ill with tuberculosis in 2019, a number that has been declining slowly in recent years. An estimated 1.2 million deaths caused by tuberculosis occurred among HIV-negative people in 2019 and an additional 208 000 deaths among HIV-positive people. Men (aged ≥ 15 years) accounted for 56% of the people who developed TB in 2019, women

accounted for 32% and children (aged < 15 years) for 12%. Of all those affected by tuberculosis, 8.2% were people living with HIV (*1*).

About a quarter of the world's population is infected with *Mycobacterium tuberculosis*, with the life-time risk of developing tuberculosis disease of about 5–10% among those infected (*2*). Tuberculosis preventive treatment is available for people with tuberculosis infection. Prevention of new infections of *M. tuberculosis* and their progression to tuberculosis disease is critical to reduce the burden of ill health and death caused by tuberculosis, and to achieve the End TB Strategy targets set for 2030 and 2035. Current health interventions for tuberculosis prevention, in addition to tuberculosis preventive treatment, include the prevention of transmission of M. tuberculosis through infection prevention and control, and vaccination of children with the bacille Calmette–Guérin (BCG) vaccine.

Tuberculosis preventive treatment reduces the risk of progression from tuberculosis infection to tuberculosis disease by about 60% but this reduction can be as high as 90% among certain high-risk groups, such as people living with HIV (*3*,*4*). Systematic tuberculosis preventive treatment is currently recommended by WHO for: household contacts of bacteriologically confirmed pulmonary tuberculosis patients, people living with HIV, people with silicosis, people receiving dialysis or antitumour necrosis factor treatment and people preparing for haematological or organ transplantation. Depending on the country context, people with risk factors other than those mentioned above (such as prisoners, non-household close contacts and people with diabetes) can also be considered for systematic screening and tuberculosis preventive treatment. At the first UN high-level meeting on tuberculosis in 2018, Member States committed to providing tuberculosis preventive treatment to at least 30 million people in the 5-year period 2018–2022, including 6 million people living with HIV, 4 million children aged under 5 years who are household contacts of people with bacteriologically confirmed tuberculosis, and 20 million household contacts in older age groups.

Summary of evidence: benefits (from the application)

Evidence for the benefits of rifapentine and isoniazid as tuberculosis preventive treatment was reviewed in 2015 (*5*).

The effectiveness of the single-pill combination formulation is expected to be similar to the combination use of the individual medicines as separate formulations.

In general, providing tuberculosis preventive treatment to high-risk individuals prevents morbidity and mortality at the individual level and reduces the tuberculosis burden by limiting its transmission from individuals who would otherwise develop tuberculosis. Recent epidemiological data from the

WHO South–East Asia region indicate that tuberculosis disease prevention at scale is an essential intervention if the End TB Strategy targets are to be met. Optimal implementation of tuberculosis preventive treatment alone in certain high-risk groups, such as household contacts or people living with HIV, has the potential to reduce the annual tuberculosis incidence rate by 8.3% (95% credible interval (CrI) 6.5 to 10.8) relative to 2015, in the absence of any additional interventions (*6*, *7*).

Summary of evidence: harms (from the application)

Evidence for the harms of rifapentine and isoniazid as tuberculosis preventive treatment was reviewed in 2015 (*5*).

The harms associated with the single-pill combination formulation are expected to be similar to combination use of the individual medicines as separate formulations.

Additional evidence (not in the application)

Not applicable

WHO guidelines

Regimens including rifapentine and isoniazid for tuberculosis preventive treatment are recommended by WHO in the 2020 WHO consolidated guidelines on tuberculosis (*8*, *9*).

The following options are recommended regardless of HIV status:

- 6 or 9 months of daily isoniazid, or
- a 3-month regimen of weekly rifapentine plus isoniazid, or
- a 3-month regimen of daily isoniazid plus rifampicin, or
- a 1-month regimen of daily rifapentine plus isoniazid, or
- a 4-month regimen of daily rifampicin.

The proposed single-pill formulation is primarily targeted for use in the 3-month weekly dosing regimen in individuals older than 14 years, in whom the recommended weekly dose is 1200 mg rifapentine + 900 mg isoniazid. The single-pill combination formulation would reduce the weekly pill burden for patients from nine tablets a week (3 x isoniazid 300 mg plus 6 x rifapentine 150 mg) to three tablets a week (*9*).

Costs/cost–effectiveness

The median cost per person treated for drug-susceptible tuberculosis in 2019 was US$ 860 and about US$ 5660 for treatment of multidrug-resistant tuberculosis (*1*). Recent modelling work in the WHO South-East Asia region

showed that the number of individuals at high risk of tuberculosis disease who need preventive treatment to avert one tuberculosis case is 64 (95% CrI 55 to 74) which is considered an attractive public health proposition (*7*). Tuberculosis preventive treatment can result in useful savings for the individual and the health system by avoiding the need for tuberculosis treatment, given the longer isoniazid monotherapy regimens needed for tuberculosis disease treatment. Further reductions in the cost of rifapentine will make this tuberculosis preventive treatment even more cost-effective. The standard regimen of 6 months isoniazid monotherapy has been the most widely used tuberculosis preventive treatment option, costing US$ 4–6 for a patient course. However, the uptake and completion of tuberculosis preventive treatment with this longer regimen has been limited (*10*).

Furthermore, WHO considers the 3-month regimen of weekly rifapentine + isoniazid and 1-month regimen of daily rifapentine + isoniazid as equivalent options for tuberculosis preventive treatment among high-risk individuals across all epidemic settings. Individuals on shorter regimens were shown to be 1.5–3 times more likely to complete treatment, which is important to maximize its effectiveness in preventing active tuberculosis (*11*–*14*). In published literature, the cost–effectiveness of the two rifapentine-containing regimens has primarily been studied in high-income, low-burden settings using the price of Sanofi-branded rifapentine (Priftin). In high-burden, low-resource settings, researchers have found the 3-month regimen of weekly rifapentine + isoniazid with directly observed therapy prevents the greatest number of tuberculosis cases compared with other regimens for latent tuberculosis infection, but at a cost of US$ 9402 per disability-adjusted life year (DALY) averted (*15*). If the price of rifapentine were reduced to US$ 8, the researchers estimated the incremental cost–effectiveness ratio would decrease to US$ 535 per DALY averted. Hence, although currently more costly compared to the isoniazid-only regimen, tuberculosis preventive treatment containing rifapentine is expected to be more cost-effective option for programmes.

Rifapentine although off patent, is currently only available from Sanofi, the innovator. There are no other quality-assured sources. In high-income countries, Sanofi sells the drug as a 150 mg tablet at US$ 1 per tablet or US$ 73 for a full patient course of the 3-month regimen inclusive of isoniazid. Through the Global Drug Facility, the company sells the drug for US$ 0.625 per tablet or US$ 46 per treatment course. This cost is significantly higher than the US$ 4–6 for the 6-month isoniazid regimen. Sanofi has entered into an agreement with the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID to reduce the price of rifapentine to US$ 15 per adult patient course for a select set of countries with a high burden of tuberculosis. The generic supplier, Macleods Pharmaceuticals, sells the single-pill combination of rifapentine

300 mg + isoniazid 300 mg, and has also entered into an agreement with the Global Fund and Unitaid to price the product at US$ 15 per patient course through a special agreement.

Availability

MacLeods Pharmaceuticals has filed the proposed formulation with multiple national drug regulatory authorities, including countries with a high burden of tuberculosis such as India and South Africa.

The formulation has been submitted for assessment by the WHO Prequalification Programme. It is currently endorsed for procurement by The Global Fund's Expert Review Panel meaning the product can be procured using Global Fund funds while the product undergoes prequalification review. The formulation is available to eligible countries through the Global Drug Facility. A box of 36 tablets (a single treatment for an adult patient) is US$ 15.

A second supplier is also at an advanced stage of development of a single-pill combination tablet of rifapentine 300 mg plus isoniazid 300 mg. The supplier has successfully completed stability and pilot bioequivalence studies on the prototype product. Once 6 months of stability information is available, the product will be submitted to WHO Prequalification Programme and the Global Fund's Expert Review Panel. The Expert Review Panel makes recommendations to the Global Fund to allow procurement while a product is undergoing quality assurance review by WHO. Rifapentine + isoniazid single-pill combination is a priority product for review by the Expert Review Panel, meaning the recommendation could be made in as little as 6 weeks from the time of dossier submission. Thus, availability of this product on the market would be expected in late 2021. As there is currently only one supplier of a non-ideal formulation of rifapentine, a Rifapentine Consortium composed of some of the main technical and funding partners that support WHO's drive to scale-up tuberculosis preventive treatment globally was established in 2019 to allocate the very limited available supply against the increasing programmatic demand. Having additional suppliers of a more suitable formulation should help restore the normal market dynamics for rifapentine and the Rifapentine Consortium will no longer be required.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with *M. tuberculosis*, with the life-time risk of developing active disease of about 5–10% among those infected.

The Committee considered that tuberculosis preventive treatment reduces the risk of progression from tuberculosis infection to tuberculosis disease by about 60% but can be as high as 90% among certain high-risk groups. Systematic tuberculosis preventive treatment is currently recommended by WHO for target populations at high risk. Furthermore, with the commitments from governments and donors, the availability of shorter regimens is expected to facilitate uptake of tuberculosis preventive treatment.

The Committee noted that WHO recommends tuberculosis preventive treatment regimens including rifapentine in combination with isoniazid as a weekly dose for 3 months (3HP) or a daily regimen for 1 month (1HP). The Committee noted that both rifapentine and isoniazid as single agents have been included as antituberculosis medicines on the core list of the EML for several years and that the effectiveness and potential harms of the two medicines are expected to be similar for the single-pill formulations and the fixed-dose combination.

Therefore, the availability of rifapentine and isoniazid in a fixed-dose combination tablet would reduce the pill burden substantially and improve adherence to treatment. This fixed-dose combination should be primarily used in the 3HP regimen for individuals older than 14 years, but it may also be used for younger children able to swallow the dosage form. Individuals on shorter regimens were shown to be 1.5–3 times more likely to complete treatment, which is beneficial as it is important to maximize its effectiveness in preventing active tuberculosis.

The Committee noted that countries have access to different formulations (in terms of registration, affordability and supply) and adding options may increase availability and the pool of suppliers.

The Expert Committee therefore recommended adding the fixed-dose combination of isoniazid and rifapentine to the core list of the EML and EMLc for tuberculosis preventive treatment for use in line with dosing recommendations in WHO guidelines.

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Antituberculosis medicines – formulations for deletion – EML and EMLc

Antituberculosis formulations – deletion and changes	**ATC Code: various**

Proposal

Deletion of and changes to listings of various antituberculosis medicine formulations on the EML and EMLc.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and/or EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Formulations for deletion

- Ethambutol: oral liquid 25 mg/mL (EMLc)
- Isoniazid: oral liquid 50 mg/5 mL (EMLc); tablet (scored) 50 mg (EML and EMLc)
- Pyrazinamide: oral liquid 30 mg/mL (EMLc); tablet (scored) 150 mg (EML and EMLc)
- Isoniazid + pyrazinamide + rifampicin: tablet 75 mg + 400 mg + 150 mg (EML)
- Amikacin: powder for injection 100 mg, 500 mg, 1 g in vial (EML and EMLc)
- Amoxicillin + clavulanic acid: oral liquid 125 mg + 31.25 mg/5 mL (EMLc)
- Ethionamide: tablet 125 mg (EML and EMLc)
- Linezolid: injection for intravenous administration: 2 mg/mL in 300 mL bag; tablet 400 mg (EML and EMLc)
- p-aminosalicylic acid: tablet 500 mg (EML and EMLc)

Formulations for addition

- Amikacin: injection 250 mg (as sulfate)/mL in 2 mL vial (EML and EMLc)

Removal of strength ranges

- Ethambutol: tablet 100 mg to 400 mg (EML)
- Isoniazid: tablet 100 mg to 300 mg (EML and EMLc)

Core/complementary

Core and complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The WHO Global Tuberculosis department, and the Stop TB Partnership's Global Drug Facility carried out a comprehensive review of the 2019 Model Lists to examine the availability and appropriateness of the tuberculosis medicines and formulations listed, in the context of the latest available WHO recommendations on tuberculosis and procurement patterns.

Public health relevance (burden of disease)

Not applicable

Summary of evidence: benefits (from the application)

In 2019, the Expert Committee recommended the addition of several new formulations for tuberculosis medicines for use in children be added to the core list of the EMLc, including ethambutol and isoniazid 100 mg dispersible tablet formulations. The Committee acknowledged that quality-assured dispersible tablet formulations are preferred to oral liquid formulations and recommended that the oral liquid formulations of isoniazid and ethambutol be considered for removal from the Model Lists in 2021 (*1*). Thus, ethambutol, isoniazid and pyrazinamide oral liquid formulations are proposed for deletion. Ethambutol, isoniazid and pyrazinamide dispersible tablet formulations have been available from the Global Drug Facility since January 2018, March 2019 and March 2018, respectively. All are available from at least one WHO-prequalified supplier.

The single-pill combination of isoniazid + pyrazinamide + rifampicin is proposed for deletion from the EML as no quality-assured supplier of this formulation has been identified. Ethambutol-containing single-pill combinations with isoniazid, pyrazinamide and rifampicin are listed and remain a suitable

option with a lower pill burden for treatment of adults with drug-susceptible tuberculosis (*2*).

Amikacin is included in the recommendations for longer regimens to treat multidrug-resistant tuberculosis, classified in Group C (to be used to complete the regimen when medicines from Groups A and B cannot be used). Amikacin is not included in recommendations for shorter regimens for treatment of drug-resistant tuberculosis (*3*). Amikacin powder for injection formulations 100 mg, 500 mg and 1 g are proposed for deletion, because of the unavailability of quality-assured formulations (1 g), the low efficiency in dose delivery (100 mg), and the fact that these formulations (all) require reconstitution before administration and are less preferred to liquid injection formulations. The application proposed to replace the current formulations of amikacin with a 250 mg/mL in 2 mL vial liquid injection formulation, noting that this formulation is already included on the Model Lists as an Access group antibiotic, and is available from the Global Drug Facility.

Linezolid 400 mg tablet is proposed for deletion because of unavailability of quality-assured formulations. Linezolid intravenous injection 2 mg/mL is proposed for deletion because of WHO's recommendations for use of all-oral regimens to treat drug-resistant tuberculosis (*3*). The oral formulations of linezolid currently listed are suitable for treatment for both adults and children.

Ethionamide 125 mg tablet is proposed for deletion given the availability of a preferred dispersible tablet formulation of the same strength, which is included on the Model Lists. The dispersible tablet formulation is available from the Global Drug Facility, and is available from WHO prequalified suppliers.

Amoxicillin + clavulanic oral liquid (125 mg + 31.25 mg/5 mL) is proposed for deletion to consolidate the market for this medicine around the 250 mg + 62.5 mg/5mL strength formulation. This higher strength formulation is included in WHO's recommended dosing schemes (*4*) and enables appropriate dosing of children across age groups and it uses smaller volumes for administration than the formulation proposed for deletion.

The application also proposes changes to the listing for isoniazid and ethambutol tablets, to replace strength ranges with specific strength formulations. In the case of ethambutol, 100 mg and 400 mg strength formulations deliver appropriate dosing for adults and children with tuberculosis. No quality-assured formulation within the strength range of 100 mg to 400 mg that could deliver added value to patient dosing is currently available on the market. In the case of isoniazid, 100 mg and 300 mg strength formulations are suitable to achieve appropriate dosing for adults and children. A 200 mg strength tablet formulation is available and approved in Germany; however, this formulation does not deliver added value in terms of facilitating dosing for adults or children.

Summary of evidence: harms (from the application)

Not applicable

Additional evidence (not in the application)

Not applicable

WHO guidelines

The proposed changes are in alignment with recommendations in current WHO guidelines for the treatment of drug-susceptible and drug-resistant tuberculosis.

Costs/cost-effectiveness

Not applicable

Availability

Not applicable

Other considerations

Not applicable

Committee recommendations

The Expert Committee recommended the deletion of the following formulations from the EML and/or EMLc as requested in the application, noting that they are not the most appropriate formulations for the treatment of tuberculosis, which is in line with recommendations in the current WHO tuberculosis treatment guidelines.

- Amikacin: powder for injection: 100 mg, 500 mg and 1 mg (as sulfate) in vial
- Amoxicillin + clavulanic acid: oral liquid 125 mg + 31.25 mg/5 mL
- Isoniazid tablet (scored): 50 mg
- Isoniazid + pyrazinamide + rifampicin tablet: 75 mg + 400 mg + 150 mg
- Linezolid: injection for intravenous administration: 2 mg/mL in 300 mL bag; tablet 400 mg
- p-aminosalicylic acid tablet: 500 mg
- Pyrazinamide tablet (scored): 150 mg

The Committee recommended the inclusion of amikacin injection solution 250 mg/mL, noting that injection solutions are preferred over powder for injection formulations as they do not require reconstitution for administration.

To better meet the dosing needs of paediatric patients, the Committee also recommended the addition of a 100 mg/2 mL strength of amikacin injection solution.

The Committee recommended that formulation strengths rather than strengths ranges for ethambutol and isoniazid tablets be specified, as requested, to facilitate rational selection and provide better clarity for countries in making national selection decisions.

The Committee recognized that dispersible tablet formulations are the preferred child-friendly formulations and provide flexible dosing options. However, because of concerns about limited uptake and availability of dispersible-tablet formulations of ethambutol, ethionamide, isoniazid and pyrazinamide in some countries, the Committee did not recommend the deletion of the oral liquid formulations of ethambutol, isoniazid and pyrazinamide, nor the 125 mg tablet formulation of ethionamide at this time. To allow countries time to transition to the adoption of the preferred, listed dispersible-tablet formulations, the Committee advised that these formulations will be deleted from the Model Lists without further consideration in 2023, unless an application is received to support their retention.

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Antituberculosis medicines – new formulations – EML and EMLc

Ethambutol	**ATC Code: J04AK02**
Isoniazid	**ATC Code: J04AC01**
Rifampicin	**ATC Code: J04AB02**

Proposal

Inclusion of intravenous formulations of ethambutol, isoniazid and rifampicin to the EML and EMLc for the treatment of tuberculosis in patients with severe forms of the disease associated with poor outcomes, patients with acute or chronic gastrointestinal disease or malabsorption disorders, patients with severe comorbidities, and patients unable or unwilling to take oral dosage forms. Separate applications were submitted for each medicine.

Applicant

Communicable Diseases Intensive Care Association Civic Union (INCURE), Ukraine

WHO technical department

Comments on the application were provided by the WHO Global Tuberculosis Programme. As was the case in 2019, the technical department did not support the inclusion of the proposed intravenous formulations of ethambutol, isoniazid and rifampicin. It was highlighted that WHO recommends oral treatment regimens for both patients with drug-susceptible and drug-resistant tuberculosis as the preferred options. In addition, most patients with severe forms of tuberculosis, patients with severe comorbidities and patients who are unable to take oral medicines can be treated with oral formulations, if necessary, using alternative forms of administration. It was also highlighted that for adult patients with drug-susceptible tuberculosis, a four-drug regimen including isoniazid, ethambutol, rifampicin and pyrazinamide is recommended; therefore, patients would still need to take pyrazinamide orally.

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Ethambutol: injection 1000 mg/10 mL; 2000 mg/20 mL
Isoniazid: injection 100 mg/mL
Rifampicin: powder for injection 600 mg in vial

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The current applications are resubmissions of applications submitted for consideration by the Expert Committee in 2019.

In 2019, inclusion of the proposed formulations was not supported by the WHO Global Tuberculosis Programme, who in response to the applications emphasized:

- WHO recommends oral treatment regimens, ideally administered in fixed-dose combinations (where such formulations exist) for the treatment of drug-sensitive tuberculosis.
- WHO's updated treatment guidelines for multidrug-resistant and rifampicin-resistant tuberculosis, recommend that injectable agents no longer be included among the priority medicines when designing longer regimens for multidrug-resistant tuberculosis.
- In view of these WHO policy recommendations, in most tuberculosis patients, intravenous administration for first- or second-line medicines is not indicated.
- For most indications listed in the applications for intravenous formulations, patients can be treated with oral formulations, if necessary using alternative forms of oral administration.
- For adult patients with drug-sensitive tuberculosis, a four-drug regimen is recommended; therefore with only three of the four medicines available as intravenous formulations, patients would still be required to take pyrazinamide orally.

The 2019 Expert Committee did not recommend their inclusion on the Model Lists. The Committee noted that WHO guidelines recommend use of oral, preferably fixed-dose combination therapy for tuberculosis, but acknowledged that parenteral administration of tuberculosis medicines may be useful in a small number of critically unwell patients unable to tolerate oral therapy, or patients

with tuberculous meningitis. The Committee considered that the inclusion of parenteral formulations of these medicines could result in inappropriate use of parenteral therapy in patients otherwise able to take oral therapy. The Committee also noted that the global market availability of these products was limited, and the comparative cost was unknown (*1*).

Public health relevance (burden of disease)

The public health relevance of medicines for the treatment of tuberculosis is well established. Globally in 2019, an estimated 10 million people fell ill with tuberculosis, and there were 1.2 million deaths among HIV-negative people and 208 000 deaths among HIV-positive people (*2*).

The applications identified the severe forms of tuberculosis for which intravenous therapy would be indicated as miliary tuberculosis, caseous pneumonia, tuberculous meningitis, tuberculosis sepsis and tuberculosis pericarditis. In addition, it was proposed that intravenous treatment would also be suitable for patients with gastrointestinal malabsorption conditions, patients with severe comorbidities (HIV, diabetes) and patients unable or unwilling to take oral therapy. However, no information was provided on the burden of disease of these cases as a proportion of the total tuberculosis cases that would be eligible for intravenous treatment.

Extrapulmonary tuberculosis is reported to account for about 14% of tuberculosis cases worldwide, and particularly affects children and people living with HIV (*3*). Tuberculous meningitis, in particular, has been reported to account for about 1% of all tuberculosis cases worldwide and its incidence is directly related to the prevalence of pulmonary tuberculosis (*4*).

Summary of evidence: benefits (from the application)

The clinical benefits and place in tuberculosis treatment of ethambutol, isoniazid and rifampicin are well established and have been evaluated previously by the Expert Committee.

Compared with the 2019 applications, the current applications did not include any comparative clinical evidence for the benefits of the intravenous formulations of ethambutol, isoniazid and rifampicin versus oral formulations in treating severe forms of tuberculosis or in the other population groups for which listing was proposed.

As in 2019, the applications presented few pharmacokinetic data describing higher achievable peak plasma concentrations with intravenous administration compared with oral administration.

Summary of evidence: harms (from the application)

The safety profiles of ethambutol, isoniazid and rifampicin are well established and have been evaluated previously by the Expert Committee.

The applications described common adverse events associated with ethambutol, isoniazid and rifampicin. Any differences in adverse events with oral versus intravenous administration were not specified.

Additional evidence (not in the application)

A small randomized trial evaluating the effectiveness of intravenous isoniazid and ethambutol in the intensive phase of treatment of patients with tuberculous meningoencephalitis and HIV co-infection was identified during the review process (*5*). Patients were randomized to receive intravenous ethambutol and isoniazid plus oral rifampicin and pyrazinamide ($n = 23$) or the same medicines administered orally ($n = 31$) for the intensive phase of therapy (2 months), followed by oral therapy for the continuation phase. Patients in the intravenous treatment group had a significant improvement in clinical symptoms and X-ray signs compared with patients in the oral treatment group. Sputum *Mycobacterium tuberculosis* positivity in the second month of treatment was 25.0% and 76.1% in the intravenous and oral treatment groups, respectively. At 6 months, mortality was significantly greater in the oral treatment group compared with the intravenous treatment group (70.9% versus 39.1%, $P = 0.023$).

WHO guidelines

For patients with drug-susceptible pulmonary tuberculosis, the 2017 WHO guidelines recommend a 6-month rifampicin-based oral regimen (2HRZE/4HR: 2 months isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months isoniazid and rifampicin) (*6*).

The 2016 WHO target regimen profiles for tuberculosis treatment (*7*) state that oral formulations are optimal, but that intravenous formulations should also be available. It further states that intravenous formulations should be reserved for sever forms of disease such as central nervous system tuberculosis or tuberculosis sepsis.

Costs/cost–effectiveness

No comparative cost–effectiveness data were available. The applications report that the intravenous formulations are more expensive than the corresponding oral formulations, but that oral and intravenous formulations should not be considered alternatives to each other in patients with severe forms of the disease.

Availability

The proposed intravenous formulations have very limited regulatory approval and global availability.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with *M. tuberculosis*, with the life-time risk of developing tuberculosis of about 5–10% among those infected.

Ethambutol, isoniazid, and rifampicin are already included in EML as oral formulations. The Committee recognized that intravenous formulations may be useful for a subgroup of severely ill patients and those who have disorders affecting oral drug absorption. The Committee considered that intravenous isoniazid and rifampicin may be recommended in specific circumstances (e.g. tuberculous meningitis). However, the role of ethambutol in the treatment of central nervous system tuberculosis disease was more limited and other agents (e.g. fluoroquinolones and aminoglycosides) are often used instead.

The current applications were resubmissions following recommendations made in 2019 not to include these formulations on the EML. The Committee considered that the applications did not provide a clear estimate of the numbers of patients who might need intravenous therapy globally and included very little evidence on the comparative efficacy of intravenous formulations compared with oral formulations. The Committee was of the opinion that a large, simple, pragmatic trial is feasible in this setting and could provide information relevant for decision-making. Moreover, the Committee considered that intravenous formulations may carry a small increased risk (e.g. of infection, thrombosis) because of the need for venous access. The cost of intravenous formulations also appears to be higher than the cost of oral formulations, and market availability is very limited.

The Committee noted that no additional evidence was submitted that would give it reason to reach a different conclusion to the recommendation made in 2019. Therefore, the Expert Committee again recommended that intravenous formulations of ethambutol, isoniazid, and rifampicin not be included on the EML and EMLc for the treatment of severe forms of tuberculosis.

References

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Bedaquiline – new formulation – EML and EMLc

Bedaquiline **ATC Code: J04AK05**

Proposal

Inclusion of a new strength formulation of bedaquiline (20 mg tablet) on the complementary list of the EML and EMLc for the treatment of multidrug-resistant tuberculosis, and an amendment to the current age restriction associated with bedaquiline from children ≥ 6 years to children ≥ 5 years and weighing at least 15 kg.

Applicant

Janssen Pharmaceutica NV, Beerse, Belgium

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Tablet 20 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Bedaquiline 100 mg tablets were added to the complementary list of the EML in 2015 as a reserve second-line medicine for treatment of multidrug-resistant tuberculosis in adults (*1*). In 2019, bedaquiline 100 mg tablets were added to the complementary list of the EMLc for the treatment of multidrug-resistant tuberculosis in children aged 6 years and older, in line with updated WHO treatment guidelines. It was noted that the extrapolation of evidence from adult data to children suggested therapeutic bedaquiline exposure in children and no increased safety risk (*2*).

Public health relevance (burden of disease)

The public health relevance of effective treatments for multidrug-resistant tuberculosis is well established.

According to WHO's 2020 global tuberculosis report, there were an estimated 465 000 new cases of multidrug-resistant tuberculosis and rifampicin-resistant tuberculosis globally in 2019, with multidrug-resistant tuberculosis accounting for 78% of these cases. An estimated 3.3% of new tuberculosis cases and 17.7% of retreated tuberculosis cases had multidrug-resistant or rifampicin-resistant tuberculosis in 2019. In total, 333 304 people (all ages) were treated for multidrug-resistant or rifampicin-resistant tuberculosis in 2018–2019, 8986 of whom were children < 17 years (*3*).

Based on mathematical models, about 3% of children with tuberculosis are estimated to have multidrug-resistant tuberculosis. Global estimates of the burden of multidrug-resistant tuberculosis in children range from 25 000 to 32 000 incident cases annually (*4*, *5*).

Summary of evidence: benefits (from the application)

Paediatric data for bedaquiline have come from the TMC207-C211 trial (NCT02354014), which is an ongoing, open-label, phase II trial. The trial is designed to evaluate the pharmacokinetics, safety, tolerability and antimycobacterial activity of bedaquiline in combination with a background regimen of multidrug-resistant tuberculosis medications in children and adolescents 0 months to < 18 years of age who have confirmed or probable pulmonary multidrug-resistant tuberculosis (*6*). The application presented data from the week 24 primary analyses of cohort 1 (≥ 12 to < 18 years, using bedaquiline 100 mg tablets) and cohort 2 (≥ 5 to < 12 years, using bedaquiline 20 mg tablets).

Cohort 1 included 15 patients with multidrug-resistant tuberculosis aged 12 to < 18 years, with baseline bodyweight ranging from 38 kg to 75 kg. These patients received bedaquiline 100 mg tablets at the recommended adult dose (400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks) in combination with a background regimen. Pharmacokinetic parameters of bedaquiline in this cohort were comparable to those in adults. In a subset of patients with culture-positive pulmonary multidrug-resistant tuberculosis at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 75% (6/8) of patients at week 24.

Cohort 2 included 15 patients with multidrug-resistant tuberculosis aged 5 years to < 12 years, with baseline bodyweight ranging from 14 kg to 36 kg. These patients received bedaquiline 20 mg tablets at a dose of 200 mg once daily for 2 weeks, followed by 100 mg three times a week for 22 weeks, in combination with a background regimen. Complete pharmacokinetic data were obtained for 10 patients. In nine of these 10 patients, the mean bedaquiline

maximum plasma concentration (C_{max}) and area under the curve at 24 hours (AUC_{24h}) were similar to that of adult patients with multidrug-resistant tuberculosis receiving the recommended adult dosage regimen. In a subset of patients with culture-positive pulmonary multidrug-resistant tuberculosis at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 100% (3/3) of patients at week 24.

Model-based pharmacokinetic analysis of bedaquiline was performed on data from patients in cohorts 1 and 2 from which the recommended dosage regimens for children and adolescents were developed.

Summary of evidence: harms (from the application)

The safety assessment of bedaquiline presented in the application was based on the week 24 analysis of 30 paediatric patients in cohorts 1 and 2 (*6*).

In cohort 1, overall, safety was generally consistent with observations from previous clinical studies with bedaquiline in adults. The most common adverse reactions were arthralgia in 6/15 (40%) patients, nausea in 2/15 (13%) patients and abdominal pain in 2/15 (13%) patients. No deaths occurred among the 15 patients during treatment with bedaquiline. Observed laboratory abnormalities were comparable to those in adults.

In cohort 2, the most common adverse reactions were related to increased aminotransferases, including from hepatoxicity (3/15, 33%), which led to discontinuation of bedaquiline in three patients. Elevations in liver enzymes were reversible on discontinuation of bedaquiline and some of the background regimen drugs. No deaths occurred among these 15 patients. The bedaquiline dosing regimen for 24 weeks as part of multidrug-resistant tuberculosis therapy was generally safe and anticipated toxicities were manageable with careful monitoring and modifications of the tuberculosis treatment regimen.

Additional evidence (not in the application)

A 2018 study evaluated the relative bioavailability, safety, acceptability and palatability of bedaquiline 100 mg tablets suspended in water compared with intact tablets (*7*). Bioavailability of the 100 mg tablet was not altered when crushed and suspended in water before administration and the suspension was well tolerated. These findings suggest that the 100 mg tablet formulation may also be suitable for administration to children unable to swallow intact tablets.

WHO guidelines

The 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment (*8*) recommend that bedaquiline may be included in longer multidrug-resistant tuberculosis regimens for patients aged 6–17 years (conditional recommendation, very low certainty in the estimates of effect). The recommended weight-based

regimen for patients 15–29 kg is 200 mg daily for 2 weeks, followed by 100 mg three times a week for 22 weeks.

The 2020 WHO consolidated guidelines on tuberculosis treatment note that the US Food and Drug Admiration has extended approval for the use of bedaquiline for children aged 5 years and older (*9*). However, these data have not yet been assessed by WHO.

Costs/cost–effectiveness

Janssen Pharmaceutica, N.V. has a long-term agreement with the International Dispensary Association for the supply of bedaquiline by order and account of the Stop TB Global Drug Facility. The Global Drug Facility is an initiative that provides a unique package of services, including technical assistance in tuberculosis drug management and monitoring of tuberculosis drug use, to patients in need in over 135 countries. To improve lead time for delivery to countries the Global Drug Facility has setup a strategic rotating stockpile, with unassigned stock always available at the International Dispensary Association.

Bedaquiline 20 mg is accessible through Global Drug Facility for US$ 25.53 for a bottle of 60 tablets. This equates to a price of US$ 200.00 for a full treatment cycle (470 tablets over 24 weeks) in children weighing 15 kg to < 30 kg, i.e. administering half the adult dose. Bedaquiline 20 mg tablet is also indicated for adults and/or adolescents who have trouble swallowing, for which a complete treatment cycle would require 940 tablets and cost US$ 400.

Janssen has made bedaquiline 100 mg tablets available through the Global Drug Facility at a price of US$ 340 for a 6-month treatment course (at the adult dose) for more than 135 eligible countries. The company will also provide an escalating percentage of free goods when certain volume thresholds are reached on an annual basis: 10% above 55 000 treatment courses, 20% above 125 000 and 30% above 200 000 (*10*).

Availability

As the 20 mg tablet formulation of bedaquiline only received US Food and Drug Administration approval on 27 May 2020, the total distribution of this formulation has been limited so far.

Other considerations

Bedaquiline 20 mg tablets are functionally scored tablets that can be administered by four different methods.

- swallowed whole, or divided in half, with water for patients able to swallow intact tablets;
- dispersed in water (maximum five tablets in 5 mL water) for patients unable to swallow intact tablets;

- crushed and mixed with soft food;
- dispersed in water (five tablets in up to 50 mL water) and administered via nasogastric tube.

The pill burden for the 20 mg tablet is high for patients of body weight ≥ 30 kg, considering the adult dosage of 400 mg (20 tablets) daily for 2 weeks, followed by 200 mg (10 tablets) three times per week for 22 weeks. Thus, the adult dose would be achieved more conveniently with the 100 mg tablets.

Committee recommendations

The Expert Committee recognized the importance of the availability of age-appropriate, child-friendly formulations of medicines for the treatment of multidrug-resistant tuberculosis to meet the dosing and administration needs of children.

The Expert Committee noted bedaquiline, as an oral 100 mg tablet formulation, was included on the complementary list of the EML as a reserve second-line medicine for treatment of multidrug-resistant tuberculosis in adults in 2015. In 2019, it was added to the complementary list of the EMLc as a reserve second-line medicine for the treatment of multidrug-resistant tuberculosis in children aged 6 years and older.

The Committee noted the acceptable pharmacokinetic data indicating therapeutic bedaquiline exposure at the recommended dose in children using the proposed 20 mg tablets formulation.

The Committee therefore recommended the addition of the new formulation of bedaquiline 20 mg tablets to the complementary list of the EMLc for the treatment of multidrug-resistant tuberculosis in children aged 5 years and older, in line with the updated WHO treatment guidelines.

The Committee did not recommend the addition of this formulation to the EML for the treatment of adults, noting the high pill-burden required to achieve the recommended adult dose. The Committee also noted that the bioavailability of the 100 mg tablet formulation, when crushed or suspended in water, was not altered. The Committee considered that the 100 mg tablet formulation, crushed or suspended in water, was a suitable alternative for adult patients unable to swallow intact tablets and allowed achievement of the recommended dose with a much lower pill burden.

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Delamanid – new formulation – EMLc

Delamanid **ATC Code: J04AK06**

Proposal

Inclusion of a new strength formulation of delamanid (25 mg dispersible tablets) on the complementary list of the EMLc for the treatment of multidrug-resistant tuberculosis; and change to the current age restriction associated with the listing from ≥ 6 years to ≥ 3 years.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strength(s)

Tablet (dispersible) 25 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Delamanid 50 mg tablets were added to the EMLc in 2017 for the treatment of multidrug-resistant tuberculosis in children aged 6–17 years (*1*). In 2019, a request to change the age restriction to ≥ 3 years was not recommended because it was noted that: the pharmacokinetic data used to inform WHO guideline recommendations used a 25 mg tablet formulation that differed from the formulation included in the Model Lists; the 25 mg formulation was not commercially available and had not been shown to be bioequivalent to the listed 50 mg formulation (*2*).

Public health relevance (burden of disease)

It is estimated that 7.5 million children and young adolescents (0–14 years) are infected with *Mycobacterium tuberculosis* each year across the world (*3*). The estimated incidence of tuberculosis disease in children younger than 15 years was 1.2 million in 2019. Globally, the number of tuberculosis notifications among children and young adolescents aged 0–14 years increased from fewer than 400 000 in 2015 to 523 000 in 2019. It is estimated that 230 000 children 0–14 years died from tuberculosis in 2019, with 80% of these deaths happening in children under 5 years. Children treated for tuberculosis have excellent outcomes (84% treatment success rate in the 2018 patient cohort) but, without treatment, mortality from tuberculosis is as high as 43% among children under 5 years of age (*4*).

More than 30 000 incident cases of multidrug-resistant tuberculosis in children are estimated globally each year. In 2020, for the first time, countries reported the number of children and young adolescents aged 0–14 years started on second-line treatment for multidrug-resistant tuberculosis and rifampicin-resistant tuberculosis: the numbers were 3398 in 2018 and 5586 in 2019 (*4*). These figures correspond to 2.2% and 3.2% of all people started on treatment for multidrug-resistant and rifampicin-resistant tuberculosis (*4*).

In September 2018, heads of state agreed on the following main global targets: 40 million people with tuberculosis to be reached with care during 2018 to 2023 (including 3.5 million children), and 1.5 million people with drug-resistant tuberculosis (including 115 000 children) (*5*). However, data in the latest global tuberculosis report in 2020 show that we are far from reaching these targets, especially for children with tuberculosis The total number of children treated for multidrug-resistant and rifampicin-resistant tuberculosis in 2018–2019 was 8986, which corresponds to only 7.8% of the 5-year target of 115 000 (*4*).

The roadmap towards ending tuberculosis in children and adolescents, launched just before the United Nations General Assembly High-Level Meeting on the Fight Against Tuberculosis, includes milestones to reaching these targets, including access to shorter and safer child-friendly regimens for prevention and treatment of drug-susceptible and drug-resistant tuberculosis. Child-friendly formulations of tuberculosis medicines are essential to facilitate correct implementation of WHO recommendations for the prevention and treatment of tuberculosis in younger children (*6*).

Delamanid is an essential medicine for young children with multidrug-resistant and rifampicin-resistant tuberculosis and extensively-drug-resistant tuberculosis, a more severe form of drug-resistant-tuberculosis. In many low-resource settings, delamanid is often used to replace painful injectable agents, which have several side-effects, when designing all-oral regimens for young children (*7*). As shown by the results of a recent survey of policies and practice

on tuberculosis prevention, testing and treatment in 37 countries with high tuberculosis burden, countries are transitioning to injectable-free, all-oral regimens for children with uncomplicated drug-resistant tuberculosis. Among the countries surveyed, 72% had policies indicating the use of oral regimens for children (*7*), with most of the regimens reported including delamanid (*8*).

Summary of evidence: benefits (from the application)

The potential benefits of delamanid were extensively reviewed and summarized at the time of the original applications and the associated evidence is available in the technical reports of the meetings (*1*, *9*).

Since the time of the original application in 2015, WHO assessed the relative effectiveness of second-line medicines for multidrug-resistant tuberculosis during a meeting of a guideline development group. As reported in the 2020 WHO consolidated guidelines on tuberculosis, the adjusted odds ratio (aOR) for delamanid was 1.1 (95% confidence interval (CI) 0.4–2.8) for treatment failure and relapse versus treatment success and aOR 1.2 (95% CI 0.5–3.0) for death versus treatment success (*10*).

Based on the pharmacological and safety data reviewed by the WHO guideline development group in 2018, including cohorts of patients 3–5 years treated with delamanid 25 mg dispersible tablet (*11*), it was concluded that exposure profiles in children given this formulation were comparable to adults and no safety signs distinct from those reported in adults were observed (*12*).

Summary of evidence: harms (from the application)

The harms associated with delamanid were reviewed and summarized at the time of the original applications and the associated evidence is available in the technical reports of the meetings (*1*, *9*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

The 2020 WHO guidelines on tuberculosis recommend that delamanid may be included in the treatment of multidrug-resistant and rifampicin-resistant tuberculosis in children aged 3 years or older on longer regimens (conditional recommendation, moderate certainty in the estimates of effect) (*10*).

Delamanid is currently classified by WHO as a Group C drug for the treatment of multidrug-resistant and rifampicin-resistant tuberculosis as part of longer regimens. Group C drugs are to be used in a treatment regimen when medicines from Groups A and B cannot be used (*10*). Delamanid is one of only a few new tuberculosis medicines that have been approved by stringent regulatory

authorities in the past few years and was first recommended for use by WHO in 2014, when the Organization issued interim policy guidance on its use. The interim policy guidance stated that "delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB" (*13*). In 2016, the delamanid interim policy was extended to children aged 6–17 years, following a review of data from a 6-month safety, efficacy and pharmacokinetic trial of paediatric patients (*14*). In January 2018, WHO issued a position statement on the use of delamanid in the treatment of multidrug-resistant tuberculosis (*15*). Based on a review of data, an expert review panel concluded that the interim and conditional guidance on delamanid should remain in place. In 2018, additional paediatric data on the use of delamanid were reviewed to examine whether the recommendations for the use of delamanid in children could be further lowered to children younger than 6 years. The focus of this review was on safety and pharmacological exposure data available from ongoing paediatric studies. At this time, WHO convened a guideline development group which reviewed the data and recommended that delamanid could be safely used in children aged 3 years and older (*11*).

However, at the time, the guideline development group also noted their concerns about the feasibility of administering the correct dose to children aged 3–5 years, given that the special formulation used in the trial (i.e. a 25 mg dispersible tablet formulation) would not be available in the foreseeable future. At that time, only the adult tablet was available (i.e. 50 mg tablet), and based on the data assessed, there were concerns that bioavailability may be altered if the 50 mg tablet was halved, crushed or dissolved. The delamanid 50 mg tablet and 25 mg dispersible tablet formulations are not bioequivalent. In a crossover bioequivalence study, neither C_{max} (90% CI of the geometric mean ratio (GMR) 0.701 to 0.809) nor AUC (90% CI GMR 0.775 to 0.909) satisfied the criteria for bioequivalence as specified by regulatory agencies. As such, the formulations are not interchangeable (*12*). Substituting the adult formulation for the paediatric formulation will result in higher delamanid exposures than would be expected from the paediatric formulation. Delamanid 50 mg tablet is also susceptible to oxidation and heat. Therefore, retaining pill fragments for use at any time other than at the time of administration will likely result in the delivery of lower-than-expected active compound and unspecified oxidation by-products. Broken 50 mg tablets were also noted to be bitter and unpalatable (*12*).

Despite these problems, clinicians and paediatric experts in the field have been manipulating the 50 mg delamanid formulation (either by splitting the tablet and then discarding the remaining part, or by giving the 50 mg tablet once a day so no manipulation of the tablet is required), as this is the only option currently available when delamanid is used in young children (Furin J, Garcia-Pratts AJ, Schaff S. Personal communication with Tiziana Masini, WHO, December 2020).

Many countries are already using delamanid as part of short, all-oral regimens under operational research conditions (*8*).

Costs/cost–effectiveness

Since April 2019, delamanid 25 mg dispersible tablets have been made available for compassionate use and can be obtained from the manufacturer (Otsuka Pharmaceuticals) at no charge on a patient-by-patient basis (*16*).

Delamanid 50 mg tablets are available via the Global Drug Facility at a price of US$ 1700 for 672 tablets (24 weeks treatment).

Availability

In September 2020, the Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion on the use of delamanid to treat pulmonary multidrug-resistant tuberculosis in adolescents and children weighing at least 30 kg (*17*). Otsuka is expecting an opinion from the Committee for Medicinal Products for Human Use for children weighing less than 30 kg in the coming months and approval of the delamanid 25 mg dispersible tablet formulation in late 2021 (Destito M, Otsuka. Personal communication with Tiziana Masini, WHO, December 2020).

Delamanid 25 mg dispersible tablets are included in the 23rd Invitation to Manufacturers of the Global Fund's Expert Review Panel to submit an expression of interest for product evaluation (*18*). Otsuka is exploring potential submission to the Global Fund ERP in 2021 (Destito M, Otsuka. Personal communication with Tiziana Masini, WHO, December 2020).

Other considerations

Not applicable

Committee recommendations

The Expert Committee recognized the importance of the availability of age-appropriate, child-friendly formulations of medicines for the treatment of multidrug-resistant tuberculosis to meet the dosing and administration needs of children.

The Expert Committee noted delamanid, as an oral 50 mg tablet formulation, has been included in the complementary list of the EML since 2015 and EMLc since 2017 for children aged 6 years and older.

The Committee noted the acceptable pharmacokinetic data indicating therapeutic delamanid exposure at the recommended dose in children using the proposed 25 mg dispersible tablet formulation, and that there were no additional safety signals beyond those already known in adults.

The Expert Committee therefore recommended the addition of the new formulation of delamanid (delamanid 25 mg dispersible tablets) to the

complementary list of the EMLc for the treatment of multidrug-resistant tuberculosis in children aged 3 years and older, in line with the updated WHO treatment guidelines.

The Committee noted that the availability of the proposed formulation was currently limited, but welcomed the intention of the manufacturer to make this formulation available through the Global Drug Facility.

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6.3 Antifungal medicines

Echinocandin antifungals – addition – EML and EMLc

Anidulafungin	**ATC Code: J02AX06**
Caspofungin	**ATC Code: J02AX04**
Micafungin	**ATC Code: J02AX05**

Proposal

Addition of echinocandin antifungals on the complementary list of the EML and EMLc for the treatment of fungal infections.

Applicant

Global Action Fund for Fungal Infections (GAFFI)

WHO technical department

Global Coordination and Partnership (Division of Antimicrobial Resistance)
Surveillance, Prevention and Control (Division of Antimicrobial Resistance)

EML/EMLc

EML and EMLc

Section

6.3 Antifungal medicines

Dose form(s) & strength(s)

Anidulafungin: lyophilized powder for infusion 100 mg
Caspofungin: powder concentrate for infusion solution 50 mg, 70 mg (as acetate)
Micafungin: powder for infusion 50 mg, 100 mg (as sodium)

Core/complementary

Complementary

Individual/square box listing

Micafungin with a square box including anidulafungin and caspofungin as therapeutic alternatives.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Echinocandin antifungals had not previously been considered for inclusion on the EML and EMLc.

In 2017, the Expert Committee recommended the inclusion of itraconazole and voriconazole to the core list of the EML and EMLc for treatment and prophylaxis of various invasive fungal infections. Voriconazole was specifically listed for the treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis (*1*). The EML and EMLc also include amphotericin B, fluconazole and nystatin for the indication of candidosis.

Public health relevance: (burden of disease)

Invasive candidiasis

Invasive candidiasis refers to bloodstream infections and deep-seated organ infections caused by *Candida* spp. (Infections concerning only the skin or mucosal surfaces thus do not fall into this category, e.g. oesophageal candidiasis, a common opportunistic infection in HIV patients with low CD4 counts.) An increasing proportion of invasive candidiasis cases is caused by azole-resistant strains of *Candida* spp. (*2*).

Invasive candidiasis is more common at the extremes of age (premature infants and older people). Several risk factors have been reported, notably intravascular catheters (for bloodstream infections), immunocompromised status (especially neutropenia), diabetes, renal dysfunction, previous antibiotic exposure (especially broad-spectrum antibiotics for prolonged durations), parenteral nutrition and prolonged stay in an intensive care unit (*3*, *4*). The global incidence of invasive candidiasis is estimated to range from 934 800 to 2 243 500 cases a year.

Up to 40% of patients with secondary or tertiary peritonitis may develop intra-abdominal candidiasis, another subtype of invasive candidiasis (*5*–*8*). Diagnosis of intra-abdominal candidiasis is difficult as there are no specific clinical signs and blood cultures are usually negative (*9*). Considering these limitations, the estimated worldwide burden of these infections ranges from 60 000 to 100 000 cases a year (*4*) with an average global incidence of 1.15 cases/100 000 inhabitants: 5.0/100 000, 4.6/100 000, 1.5/100 000 and 1.4/100 000 in Mexico, Germany, Nigeria and Spain, respectively (*10*–*13*).

One of the associated syndromes in patients with haematological malignancy is chronic disseminated candidiasis. This syndrome is a relatively rare infection but is more common if antifungal prophylaxis is not routinely given in patients with leukaemia (*14*–*16*).

Candidaemia, a specific subtype of invasive candidiasis, is one of the most common hospital-associated bloodstream infections; it has been the fourth to the seventh cause of hospital-associated bloodstream infections worldwide for more than 15 years. The incidence of bloodstream infections related to intravascular devices (IVD) ranges from 0.5/1000 IVD-days to 2.7/1000 IVD-days depending on the catheter type and setting, and *Candida* spp. are

a frequent cause (*17*). More than 70% of the cases of candidaemia in non-neutropenic patients are associated with intravascular devices (*18–21*). These infections arise because of the ability of *Candida* spp. to form biofilms on foreign bodies such as intravascular catheters (*22*, *23*). The incidence of candidaemia is lowest in very low-income countries and in high-income countries such as Australia, Canada, New Zealand, and countries in northern Europe, and highest in middle-income countries such as Brazil, India and Pakistan (*4*). The global burden of candidaemia is estimated to be between 5 and 12/100 000 population, or between 374 000 and 897 410 cases a year; short-term mortality ranges from 46% to 75% (the attributable mortality is probably much lower) (*4*, *24–26*).

Non-invasive candidiasis

The annual incidence of oesophageal candidiasis in the population not infected with HIV is difficult to estimate. A global total of about 1.6 million cases a year of oesophageal candidiasis is considered likely (*27*).

Invasive aspergillosis

Aspergillus spp. are the most common filamentous fungal pathogens. These pathogens usually affect patients with underlying immunosuppression (e.g. people with leukaemia, lymphoma, lung cancer, advanced HIV disease, and organ transplant recipients), chronic pulmonary diseases (e.g. chronic obstructive pulmonary disease) or concomitant viral infections in critically-ill, intubated patients (e.g. influenza, severe acute respiratory syndrome coronavirus 2). In leukaemia, lung cancer, HIV and chronic obstructive pulmonary disease, the global minimum annual incidence is 860 000. With other risk groups not accounted for, the total global annual incidence is likely to be > 1 million. Invasive aspergillosis is almost always fatal unless treated (*28*, *29*).

Chronic pulmonary aspergillosis in non-immunocompromised patients

The annual incidence and 5-year period prevalence of chronic pulmonary aspergillosis has been estimated at 372 000 and 1 174 000 (*30*). A recent prospective study in Uganda of patients 2 to 7 years after completing antituberculosis treatment found an equal number of cases of chronic pulmonary aspergillosis in people with and without HIV infection (*31*). According to a study from Indonesia, 13% of patients had chronic pulmonary aspergillosis at the time of finishing their antituberculosis therapy (*32*).

Summary of evidence: benefits (from the application)

Echinocandins are fungicidal against most *Candida* spp. and show in vitro activity against some filamentous fungi including *Aspergillus* spp. (*33*). These medicines act by inhibiting the production of the main component of the cell wall of ascomycete fungi – β 1,3-glucan, a molecule absent in mammalian cells

(*34*–*36*). Echinocandins are not substrates of fungal efflux pumps, which makes them active against fungal strains with overexpression of these pumps (a key mechanism of azole antifungal resistance) (*37*, *38*).

The European Medicines Agency has approved micafungin for treatment of invasive candidiasis and prophylaxis against *Candida* infections in neutropenic patients (< 500 neutrophils/μL for ≥ 10 days) for adults and children. The use of micafungin to treat oesophageal candidiasis is only indicated for adults (*39*). Caspofungin is approved for treatment of invasive candidiasis and invasive aspergillosis that are not responsive to the usual therapeutic dose and/or for treatment of invasive aspergillosis in patients unable to take amphotericin B and/or itraconazole (*40*). Anidulafungin is approved for *Candida* infections (candidaemia, intra-abdominal abscess and peritonitis) and oesophageal candidiasis (*41*).

General considerations

In clinical practice, treatment of fungal infections is often empirical since the invasive procedures potentially required to make a microbiological diagnosis are often thought to be have too many risks in severely ill patients. This complicates making a definitive diagnosis and makes it difficult to determine objective microbiological endpoints in clinical studies. For this reason, the initial studies on echinocandins were conducted for oesophageal candidiasis, where treatment efficacy can be relatively easily evaluated (through endoscopy and/or biopsy) and a large number of potentially eligible patients are available (*42*, *43*).

As a general overview of all the data analysed in the application, the authors stated that "Echinocandins are better than or at least as efficient as different comparators for all the described *Candida* infections including oesophageal candidiasis, candidaemia, different forms of invasive candidiasis and infections caused by different *Candida* species. Moreover, some good results were obtained for echinocandins as treatment options in the paediatric population and as prophylaxis and empiric therapy for invasive candidiasis in different immunosuppressed populations. Echinocandins are recommended as salvage therapy for aspergillosis that is refractory to approved therapy (amphotericin B and *Aspergillus* active azole agents)".

Oesophageal candidiasis

In the three randomized trials identified, the cure rate with echinocandins was similar or better than treatments with comparator drugs (amphotericin B or fluconazole) (*42*, *44*, *45*). The studies drew the following conclusions.

- Caspofungin appeared to be as effective as and better tolerated than amphotericin B for the treatment of oesophageal candidiasis (*42*).

- At the end of therapy, the rate of endoscopic success for anidulafungin (242/249 patients treated; 97.2%) was statistically non-inferior to that for fluconazole (252/255 patients treated; 98.8%): treatment difference –1.6%; 95% confidence interval (CI) –4.1 to 0.8 (*44*).
- The endoscopic cure rate for 100 mg and 150 mg of micafungin per day (83.5%) was comparable to that of 200 mg of fluconazole per day (86.7%); 95% CI for the difference in endoscopic cure rate –14.0% to 7.7% (*45*).

Candidaemia and common forms of invasive candidiasis

Five randomized trials were included in the analysis. Two trials compared micafungin and caspofungin for invasive candidiasis. In one of these trials, dosages of micafungin 100 mg daily and 150 mg daily were non-inferior to a standard dosage of caspofungin for the treatment of candidaemia and other forms of invasive candidiasis (*46*), and the other trial found that the efficacy of caspofungin and micafungin was similar (*47*).

Three randomized trials compared echinocandins with amphotericin B or fluconazole and reported the following:

- Caspofungin was as effective as amphotericin B in patients with candidaemia, with a favourable response in 71.7% and 62.8% of patients, respectively (difference, 10.0 percentage points, 95% CI –4.5 to 24.5) (*48*).
- Treatment success was observed for 181 (89.6%) patients receiving micafungin and 170 (89.5%) patients treated with liposomal amphotericin B. After stratification by neutropenic status at baseline, the difference in proportions was 0.7% (95% CI –5.3 to 6.7). Micafungin was as effective as liposomal amphotericin B as first-line treatment of candidaemia and invasive candidiasis, and caused fewer adverse events (*49*).
- At the end of intravenous therapy, treatment was successful in 75.6% of patients receiving anidulafungin, compared with 60.2% of patients treated with fluconazole (difference 15.4 percentage points, 95% CI 3.9 to 27.0). The results were similar for other efficacy endpoints. Anidulafungin was non-inferior to fluconazole in the treatment of invasive candidiasis (*50*).

The application noted that when fluconazole was used as a comparator, anidulafungin had a better response rate for all *Candida* spp. except *C. parapsilosis*. This showed for the first time that some *Candida* spp. would behave differently.

A recent network meta-analysis of 13 randomized trials with 3528 participants with candidaemia and/or invasive candidiasis treated with either an echinocandin (n = 1531), amphotericin B (n = 944) or an azole (n = 1053) showed that echinocandins were associated with greater treatment success than amphotericin B (odds ratio (OR) 1.41, 95% CI 1.04 to 1.92) and the azoles (OR 1.82, 95% CI 1.35 to 2.51) (*51*).

Less common forms of invasive candidiasis

A comparative study showed that the efficacy of caspofungin in uncommon infections (endocarditis, osteomyelitis, peritonitis, and chronic disseminated and septic arthritis caused by *Candida* spp.) was similar to its observed effectiveness for candidaemia (*52*).

Non-albicans Candida spp. infections

Some evidence suggests that echinocandins produce similar outcomes to other classes of antifungal agents (such as liposomal amphotericin B) independent of the *Candida* species causing the infection (*53*).

A pooled analysis of two randomized trials included one study comparing micafungin (100 mg/day) and liposomal amphotericin B, and a second study comparing different micafungin doses and caspofungin. Clinical cure rates in those receiving micafungin were similar to those randomized to the comparator (73.5% (86/117) versus 62.1% (41/66), $P > 0.05$). Mortality at 28 days was also similar (29.1% (34/117) with micafungin versus 34.8% (23/66) with the comparator, $P > 0.05$). Micafungin resulted in similar outcomes to comparators for candidaemia and invasive candidiasis caused by *C. glabrata* and *C. krusei*. The 100 mg/day dose is an acceptable option in this setting. Patient characteristics and catheter management appeared to be more important factors affecting clinical outcomes (*53*).

Prophylaxis for invasive candidiasis in different immunosuppressed populations

Two randomized trials compared the usefulness of prophylactic echinocandins against invasive candidiasis in immunosuppressed populations (*54*, *55*). In the first trial, the overall efficacy of micafungin was superior to that of fluconazole for antifungal prophylaxis during the neutropenic phase after haematopoietic stem cell transplantation (80.0% efficacy for micafungin versus 73.5% for fluconazole; 95% CI 0.9% to 12%) (*54*). In the second trial intravenous itraconazole and caspofungin gave similar protection against invasive fungal infection during induction chemotherapy (*55*).

Echinocandins as first-line treatment against invasive aspergillosis

Azoles are the drug of choice to treat invasive aspergillosis. This fungal infection is a common complication in haematopoietic stem cell transplantation

recipients. In these patients, it is difficult to keep an equilibrium between efficacy and toxicity when using regular antifungal treatments. Three randomized trials examined echinocandin efficacy and safety to treat invasive aspergillosis (*56–58*). The success rate was low with caspofungin, but better for micafungin when using voriconazole as the comparator. However, based on these trials, echinocandins have not been recommended in treatment guidelines as the primary monotherapy for the treatment of invasive aspergillosis.

Echinocandins against aspergillosis refractory to approved therapy (salvage therapy)

Invasive aspergillosis is associated with frequent treatment failures. The mortality is worse for refractory infections, especially when the antifungal is switched to a salvage monotherapy. The results of four studies were assessed.

- A non-comparative open-label trial using micafungin alone or in combination with another systemic antifungal agent (amphotericin B) was designed to show the safety and efficacy of micafungin in the treatment of acute invasive aspergillosis that had failed to respond to previous therapy. Micafungin as primary or salvage therapy was efficacious and safe in high-risk patients with invasive aspergillosis, although there were few patients in the micafungin-only group (*59*).
- A non-comparative open-label study included 53 adults with documented invasive aspergillosis refractory to standard antifungal therapy or who could not tolerate standard therapy. The participants received caspofungin and another antifungal agent (at the investigator's discretion). Caspofungin, combined with a triazole or polyene, was an effective alternative as salvage therapy for patients with refractory *Aspergillus* infections (*60*).
- A prospective multicentre study analysed a series of transplant recipients who received voriconazole + caspofungin ($n = 40$) as primary therapy for invasive aspergillosis (proven or probable). The outcomes were compared to a control group of consecutive transplant recipients treated with lipid formulation of amphotericin B. The authors concluded that a combination of voriconazole and caspofungin could be a preferable treatment for subsets of organ transplant recipients with invasive aspergillosis, for example, patients with renal failure or *A. fumigatus* infection (*61*). The study did not analyse the effect of voriconazole alone.
- A non-comparative study included 98 haematopoietic stem cell transplant recipients with invasive aspergillosis (refractory in 83) who received micafungin either alone or in combination with other

therapies. The study found that micafungin was well tolerated, even at high doses, and concluded that micafungin was a reasonable option for treatment of invasive aspergillosis in such high-risk patients (*62*).

Echinocandins in children

Data on the pharmacokinetics and safety of echinocandins in children are few.

- An ascending dosage study assessed the pharmacokinetics of anidulafungin in neutropenic paediatric patients (2–11 years and 12–17 years) and concluded that paediatric patients receiving 0.75 mg/kg/day or 1.5 mg/kg/day of anidulafungin have concentration profiles similar to those of adult patients given 50 mg/day or 100 mg/day, respectively (*63*).
- An open-label study included children with proven or probable invasive aspergillosis, proven invasive candidiasis or proven oesophageal candidiasis. All children received caspofungin 70 mg/m² on day 1, followed by 50 mg/m² per day (maximum: 70 mg/day) as primary or salvage monotherapy. Caspofungin was generally well tolerated in patients aged 6 months to 17 years. The efficacy of caspofungin in patients with invasive aspergillosis or invasive candidiasis was consistent with previous adult studies for these indications (*64*).
- A paediatric substudy was conducted of a double-blind, randomized trial to compare micafungin (2 mg/kg) with liposomal amphotericin B (3 mg/kg) as first-line treatment of invasive candidiasis. Treatment success was observed for 35/48 (72.9%) patients receiving micafungin and 38/50 (76.0%) patients receiving liposomal amphotericin B. The difference in proportions adjusted for neutropenic status was –2.4% (95% CI –20.1% to 15.3%). The authors concluded that micafungin seemed as effective and as safe as liposomal amphotericin B for treatment of invasive candidiasis in children (*65*).

The application also lists different guidelines published by European and North American infectious diseases societies and endorsed by different South American and Asian societies. These guidelines include echinocandins as the recommended first-treatment option for *Candida* spp. infections and as salvage therapy, or echinocandins in combination with other antifungals for *Aspergillus* spp. infections (*66–68*).

Summary of evidence: harms (from the application)

The main reported adverse effects of echinocandins are related to infusion reactions (e.g. phlebitis and fever), mild increases in liver enzymes, minor

hypokalaemia and unspecific signs (including gastrointestinal discomfort, headache or skin rash) (*39–41*, *69*, *70*).

Anidulafungin seems to produce fewer adverse effects than micafungin or caspofungin, although fewer studies have used this medicine. The most common reported adverse effects of anidulafungin were diarrhoea, hypokalaemia and elevated levels of alanine aminotransferase (all ≤ 3% of the patients). Compared with fluconazole, the adverse effects profile seems similar, but with a lower incidence of hepatic adverse effects among patients receiving anidulafungin (*50*). The most frequent adverse effects reported for caspofungin were infusion-related events because the solution is quite acidic. Reducing the rate of infusion or infusion using a central venous catheter may reduce these events. A comparison of caspofungin and amphotericin B in 224 patients with invasive candidiasis showed that caspofungin was better tolerated than amphotericin B. Nephrotoxicity and hypokalaemia were observed in both groups. However, they were significantly less frequent and milder in the group treated with echinocandin. Abnormalities in liver function markers were also mild and seen in only 8% of the patients treated with caspofungin (*48*). For micafungin, the most frequent adverse effects reported in clinical trials with 202 patients were infusion-related reactions, hypokalaemia, abdominal discomfort and nausea, and elevation of liver enzymes (*55*). According to the results of these three clinical studies, liver adverse effects related to echinocandin treatment (including increases in aminotransferases) are mild and less frequent than cases reported with fluconazole and amphotericin B (*48–50*).

Hepatocellular tumours in animal models

Hepatocellular tumours were observed in rat models using human therapeutic doses of micafungin. These effects were found after prolonged exposure (> 3 months) (*71*). The European Medicines Agency imposed a black box warning for micafungin and extensive phase 4 pharmacovigilance requirements (*39*). A multicentre cohort study was designed to determine the risk of fatal hepatocellular carcinoma among patients treated with micafungin and other parenteral antifungals with up to 12 years of follow-up. Both micafungin and comparator antifungals were associated with hepatocellular carcinoma mortality rates of < 0.2 per 1000 person-years. Given the very low event rates, the authors considered that any potential risk for hepatocellular carcinoma should not affect clinical decisions on treatment with micafungin or other parenteral antifungals investigated in the study (*72*).

Drug–drug interactions

Echinocandins are poor substrates for cytochrome P450 enzymes. Thus, co-administration with cytochrome P450 inhibitors or inductors (e.g. carbamazepine and phenytoin) is not clinically significant. Caspofungin may

interact with halogenated penicillins (e.g. dicloxacillin) as it potentially induces CYP3A4 enzyme (*73–76*). Clinically significant interactions with caspofungin were documented with rifampicin, tacrolimus and ciclosporin (*77–79*). Ciclosporin showed clinically significant interactions with micafungin, but this effect was not seen when coadministered with anidulafungin (*80*, *81*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

Not available

Costs/cost–effectiveness

Several pharmacoeconomic evaluations have been published comparing echinocandins with azoles (fluconazole and voriconazole), echinocandins with amphotericin B, and two of the three echinocandins with each other (summarized in Table 17 of the full application (*82*)). Limitations of these evaluations include the fact that few included the concept of life-years gained in their cost estimations and few compared one echinocandin versus other medicines of the same group. In some of the evaluations, caspofungin was cheaper and in others, micafungin was a more cost-effective option.

When lipid amphotericin B and fluconazole were compared with echinocandins, echinocandins were more cost-effective, especially in high-income countries, since the cost of health personal and other associated expenditures are higher than in low-income countries. In low- and middle-income countries, deoxycholate amphotericin B and fluconazole are regarded as more cost-effective than the echinocandins. In these countries, the main cost drivers are drug acquisition costs.

Availability

Micafungin is proposed as the representative of the echinocandin class because it is registered in more countries than caspofungin or anidulafungin. It also has the simplest dose regimen and there are data to support its use in neonates. Echinocandins are approved by different medicine agencies, including the US Food and Drugs Administration, European Medicines Agency and Japanese Medicines Agency. For caspofungin and micafungin, different approved generic products are already authorized.

Other considerations

Confirmation of the fungal etiology of infection, identification of the causative agent and ideally its susceptibility to antifungals is necessary for optimal treatment of fungal infections. Specimens for fungal cultures and other relevant

studies (wet mount, histopathology, serology, antigen detection, polymerase chain reaction testing and imaging) should be obtained for this purpose whenever possible.

Echinocandin minimum inhibitory concentrations are low for most *Candida* spp., including intrinsically azole-resistant species and strains with secondary resistance (*37*, *83*–*86*). Antifungal susceptibility testing should be performed whenever possible for any strain isolated from a normally sterile site. Echinocandin susceptibility testing can be carried out using standardized and commercially available microdilution and agar diffusion methods.

It should be noted that antifungal susceptibility testing is more difficult to perform than antibiotic susceptibility testing. Therefore such testing may be unavailable in many settings, especially in low- and middle-income countries.

Antibiotic Working Group considerations

The EML Antibiotic Working Group discussed the application during a virtual meeting on 14 April 2021. The Working Group agreed that echinocandins are efficacious medicines with fungicidal activity against most *Candida* spp. and some activity against *Aspergillus* spp. The Working Group also acknowledged that echinocandins generally have a good safety profile and that resistance to this class of antifungals remains low. The Working Group therefore supports the inclusion of echinocandins on the EML and EMLc, although for more limited indications than requested in the application.

Indications for which the Working Group supports the listing:

- Empiric treatment of suspected fluconazole -resistant candidaemia or suspected candidaemia/invasive candidiasis in critically ill patients treated in intensive care settings, especially patients with neutropenia.

Indications for which the Working Group does not support the listing:

- Invasive aspergillosis. The Working Group decided that given the weak evidence available, it does not support listing echinocandins at this time for the treatment of aspergillosis. For aspergillosis, it was noted that echinocandins are not the treatment of choice but rather salvage therapies for refractory cases and these indications are usually not addressed in the EML and EMLc, which focuses on empiric therapy.
- Prophylaxis for invasive candidiasis, as it was concluded that fluconazole remains effective in most cases.
- Oesophageal candidiasis, as it was concluded that fluconazole remains effective in most cases.

The Working Group supports the request of listing micafungin as a representative of the echinocandins class in the EML and EMLc for the reasons provided in the application (availability), noting that micafungin is not licensed for the treatment of aspergillosis. Caspofungin and anidulafungin could be listed as therapeutically equivalent alternatives so that countries have more options to choose from based on price and availability.

Committee recommendations

The Expert Committee noted that there is good evidence to support the use of echinocandin antifungals in the empiric treatment of suspected or proven invasive *Candida* infections in critically ill patients (especially where the probability of azole resistance is high). Therefore, the Committee recommended echinocandins be added to the EML and EMLc for this indication. The Committee noted that fluconazole (which can be taken orally and is substantially cheaper than echinocandins) is still effective and has a good safety profile for prophylaxis and treatment of invasive and oesophageal *Candida* infections; therefore it did not recommend listing echinocandins for these indications. The Committee acknowledged the potential role for echinocandins in the second-line treatment of invasive *Aspergillus* infections but did not recommend listing echinocandins for this indication given the availability of established alternatives.

The Committee recommended listing micafungin as the representative medicine, noting that: the patent has recently expired; micafungin is approved for use in neonates and paediatric patients; it is widely available globally; and it has the simplest dosing scheme (caspofungin and anidulafungin require loading doses). The Committee recommended anidulafungin and caspofungin be included with the listing as therapeutic alternatives, and that all three echinocandins be considered equivalent for procurement purposes.

The Committee noted that echinocandins are expensive medicines and considerably more expensive than amphotericin B and fluconazole in most settings. Furthermore, antifungal resistance is becoming an increasing problem in many settings (mostly to azoles but also described for echinocandins). The Committee therefore stressed the importance of antimicrobial stewardship activities to support the appropriate use of echinocandins.

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6.4 Antiviral medicines

6.4.2 Antiretrovirals

Antiretrovirals – formulations for deletion – EML and EMLc

Antiretroviral formulations for deletion **ATC Code: various**

Proposal

Deletion of various antiretroviral formulations from the core list of the EML and EMLc.

Applicant

WHO Global HIV, Hepatitis and STIs Programmes

WHO technical department

WHO Global HIV, Hepatitis and STIs Programmes

EML/EMLc

EML and/or EMLc

Section

6.4.2 Antiretrovirals

Dose form(s) & strength(s)

Lamivudine: tablet 150 mg (EMLc)
Abacavir: tablet (dispersible, scored) 60 mg (EMLc)
Efavirenz: tablet (scored) 200 mg (EML and EMLc)
Ritonavir: oral liquid 400 mg/5 mL (EML and EMLc); oral powder 100 mg in sachet (EMLc)
Atazanavir: solid oral dose form 100 mg (EML and EMLc); 300 mg (EML)
Lopinavir + ritonavir: oral liquid 400 mg + 100 mg/5 mL (EML and EMLc)
Raltegravir: chewable tablet 100 mg (EML and EMLc); tablet 400 mg (EMLc)
Lamivudine + nevirapine + zidovudine: tablet 30 mg + 50 mg + 60 mg (EMLc); 150 mg + 200 mg + 300 mg (EML)

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Not applicable

Public health relevance (burden of disease)

Not applicable

Summary of evidence: benefits (from the application)

Recommendations were made by the WHO HIV Department to delete the above-mentioned antiretroviral formulations from the EML and/or EMLc in order to achieve alignment between WHO's 2019 *Update of recommendations on first- and second-line antiretroviral regimens* (*1*) and *The 2021 optimal formulary and limited-use list for antiretroviral drugs for children: policy brief* (*2*).

Lamivudine tablet 150 mg and abacavir dispersible, scored tablet 60 mg are proposed for deletion from the EMLc. These formulations have been excluded from the 2021 optimal formulary since a regimen of three nucleoside/nucleotide reverse-transcriptase inhibitors for tuberculosis co-treatment is no longer needed given the introduction of dolutegravir.

Efavirenz scored tablet 200 mg is proposed for deletion from both the EML and EMLc. This formulation has been excluded from the 2021 optimal formulary as efavirenz-containing regimens are not a preferred or alternative regimen for children in the WHO guidelines (*1*). Active phase out is being supported by major procurement agencies as regimens containing efavirenz are now considered suboptimal in light of the high level of resistance to non-nucleoside reverse-transcriptase inhibitors documented in many countries. The 200 mg formulation of efavirenz is not an appropriate strength formulation for treatment of adults. Efavirenz 600 mg tablets remain on the EML for adult use.

Ritonavir oral liquid 400 mg/5 mL is proposed for deletion from both the EML and EMLc. This formulation was proposed for deletion in 2019 but was retained until the availability of alternative ritonavir formulations was established. It was recommended for deletion without further discussion by the Expert Committee in 2021 (*3*). Furthermore, this formulation is no longer necessary for lopinavir + ritonavir super-boosting, as dolutegravir is a more suitable option for tuberculosis co-treatment. Ritonavir heat-stable tablets 25 mg and 100 mg remain on both the EML and EMLc.

Ritonavir oral powder 100 mg in sachet is proposed for deletion from the EMLc. It is no longer included in the 2021 optimal formulary, and as with ritonavir oral liquid, this formulation is no longer necessary for lopinavir + ritonavir super-boosting since dolutegravir became available.

Atazanavir solid oral dose form 100 mg and 300 mg are proposed for deletion from the EML and EMLc. Single-agent atazanavir formulations require separate administration of ritonavir; therefore alternatives are preferred (e.g.

dolutegravir 10 mg or 50 mg, and solid fixed-dose formulations of lopinavir/ritonavir). Atazanavir 100 mg was excluded from the 2021 optimal formulary for this reason.

Lopinavir + ritonavir oral liquid 400 mg + 100 mg/5 mL is proposed for deletion from the EML and EMLc. This formulation has been replaced in practice by solid oral dose forms (pellets and granules), which remain on the EML and EMLc. This formulation of lopinavir + ritonavir was also excluded from the 2021 optimal formulary.

Raltegravir chewable tablet 100 mg is proposed for deletion from the EML and EMLc, and raltegravir tablet 400 mg is proposed for deletion from the EMLc. Raltegravir 100 mg chewable tablet was replaced on the 2018 optimal formulary. It was proposed for deletion from the EML and EMLc in 2019, but was retained until the availability of the 25 mg formulation was established. It was recommended for deletion without further discussion by the Expert Committee in 2021 (*3*). Raltegravir chewable tablet 25 mg and granule 100 mg remain on the EML and EMLc. Raltegravir 400 mg tablets remains on the EML.

Lamivudine + nevirapine + zidovudine fixed-dose combinations are proposed for deletion from the EML (150 mg + 200 mg + 300 mg) and EMLc (30 mg + 50 mg + 60 mg). Nevirapine-containing regimens are not recommended in WHO guidelines as a preferred or alternative regimen (*1*). Active phase out is being supported by major procurement agencies as these regimens are now considered suboptimal in light of the high level of resistance to non-nucleoside reverse-transcriptase inhibitors documented in many countries.

Summary of evidence: harms (from the application)

Not applicable

Additional evidence (not in the application)

Not applicable

WHO guidelines

The proposed deletions are in alignment with recommendations in current WHO guidelines and *The 2021 optimal formulary and limited-use list for antiretroviral drugs for children: policy brief*.

Costs/cost–effectiveness

Not applicable

Availability

Not applicable

Other considerations

Not applicable

Committee recommendations

The Expert Committee recommended the deletion from the core list of the EML and/or EMLc of the antiretroviral formulations and strengths as requested in the application.

The Committee considered the rationale behind the proposed deletions to be reasonable, and that removal of these formulations would ensure full alignment between the Model Lists and recommendations included in the most recent WHO antiretroviral treatment guidelines and *The 2021 optimal formulary and limited-use list for antiretroviral drugs for children*.

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6.4.2.4 *Integrase inhibitors*

Dolutegravir – new formulation – EMLc

Dolutegravir **ATC Code: J05AJ03**

Proposal

Inclusion of a new strength formulation of dolutegravir (10 mg dispersible tablets) on the core list of the EMLc for the treatment of HIV-1 infection in paediatric patients at least 4 weeks of age and weighing at least 3 kg.

Applicant

Clinton Health Access Initiative, Inc., United States of America

WHO technical department

WHO Global HIV, Hepatitis and STIs Programmes

EML/EMLc

EMLc

Section

6.4.2.4 Integrase inhibitors

Dose form(s) & strength(s)

Tablet (dispersible, scored): 10 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Dolutegravir 50 mg tablets were added to the core list of the EML in 2017 for treatment of adult patients with HIV-1 infection in combination with an optimized nucleoside reverse-transcriptase inhibitor (NRTI) background (*1*). In 2019, dolutegravir 50 mg tablets were added to the core list of the EMLc for treatment of paediatric patients with HIV-1 weighing 25 kg or more, in combination with an optimized NRTI background, in line with recommendations in WHO guidelines. The Expert Committee noted that the available evidence for the use of dolutegravir in children was largely limited to pharmacokinetic and

safety data from two ongoing paediatric trials, but considered that extrapolation of efficacy from adult trials was acceptable (*2*).

Public health relevance (burden of disease)

According to UNAIDS global aids update of 2020, there were 38 million people living with HIV/AIDS globally, 1.7 million new HIV-1 infections (a decrease of 23% since 2010) and 690 000 thousand HIV-related deaths. Over 95% of people infected with HIV live in low- and middle-income countries with inadequate resources to effectively combat the epidemic. While some countries have achieved declines in new HIV infections among adults of 50% or more, global data show that many other countries have not made measurable progress and some areas in Eastern Europe, central Asia, northern Africa and Latin America have experienced concerning increases in new HIV infections. Overall, about 25.4 million people were receiving antiretroviral therapy in 2019, an estimated two thirds of the people infected with HIV (*3*).

There were 150 000 new HIV infections in children aged 0 to 14 years in 2019 (*3*). Evidence shows that in the absence of antiretroviral therapy, more than 50% of HIV-infected infants progress to AIDS or death by the age of 2 years (*4*). The introduction of effective paediatric antiretroviral therapy has changed HIV infection in children from a life-threatening illness to a chronic-but-manageable infection, albeit highly dependent on good adherence to treatment. Despite recognition of the advantages of early treatment, paediatric treatment coverage still reached only 53% of children eligible for treatment in 2019 (*3*) and data consistently show children are less likely than adults to achieve viral suppression (*5*).

Antiretroviral therapy based on non-nucleoside reverse-transcriptase inhibitors has been widely used in paediatric patients for both prevention of HIV transmission and treatment. A recent survey of newly diagnosed children in five sub-Saharan African countries found resistance to one or more non-nucleoside reverse-transcriptase inhibitors in up to 53% of these children (*6*). The increasing prevalence of resistance to the previously recommended first-line antiretrovirals has prompted WHO to recommend rapid transition to dolutegravir-based treatment as formulations suitable for children become available.

Although global clinical experience with the use of dolutegravir in younger children is limited, it is recommended in this population based on extrapolation of efficacy from the larger, more diverse adult studies. Thus, the most recent WHO treatment guidelines for paediatric use of dolutegravir are based primarily on aligning pharmacokinetic data collected in clinical trials on children receiving dolutegravir to adult pharmacokinetic targets. As a result, adolescents and older children are increasingly receiving dolutegravir-based therapy using adult formulations found to be highly effective. Approval

of dolutegravir 10 mg scored, dispersible tablets will allow the use of optimal regimens in both high- and low-income settings across all paediatric age groups.

Summary of evidence benefits (from the application)

The paediatric data presented and published to date is from two ongoing clinical trials, IMPAACT P1093 and ODYSSEY. Both trials evaluated dolutegravir in paediatric patients, down to 4 weeks of age and weighing 3 kg, using a combination of dispersible tablets and film-coated tablets depending on the study participants' age, weight and ability to swallow tablets. No data are currently available to support giving dolutegravir to infants younger than 4 weeks of age (neonates) or to preterm infants.

IMPAACT P1093 is an ongoing single-arm, open-label trial of dolutegravir in children with HIV. The United States (US) Food and Drug Administration's (FDA's) initial approval of dolutegravir for use in children weighing at least 40 kg was based on data from 23 adolescents who had received antiretroviral therapy but not integrase inhibitors (12 to < 18 years) (*7*). These data have been previously described in the application for dolutegravir 50 mg to be added to the EMLc in 2019 (*2*).

Data from the P1093 trial included: cohorts 1 (12 to < 18 years) and 2 (6 to < 12 years), which provided evidence supporting the use of dolutegravir 50 mg film-coated tablets in paediatric patients weighing more than 14 kg; and cohorts 3 (2 to < 6 years), 4 (6 months to < 2 years) and 5 (4 weeks to < 6 months), which provided evidence supporting the use of dolutegravir 25 mg dispersible tablets. As the study progressed, dosing in some cohorts was adjusted to achieve the pharmacokinetic targets. Seventy-five study participants received the currently approved dose (determined by weight and age) of dolutegravir film-coated tablets or dispersible tablets. These 75 participants ranged in age from 1 to 214 months, 59% were female and 68% were black or African American. Eighty per cent of participants were treatment-experienced, but all were integrase inhibitor-naïve. Of these 75 patients who received either dolutegravir 50 mg film-coated tablets or dolutegravir 25 mg dispersible tablets according to the approved dosing recommendations for their weight band, 42 received dolutegravir for at least 48 weeks. At week 48, 69% of participants achieved HIV RNA < 50 copies/mL and 79% achieved HIV RNA < 400 copies/mL. The median CD4 count (per cent) increase from baseline to week 48 was 141 cells/mm3 (7%). The effectiveness observed in the trial was comparable to that of treatment-experienced adult patients (*8–10*).

The ODYSSEY trial enrolled both treatment-naive and treatment-experienced paediatric patients in the European Union, Thailand and several African countries; this trial initially evaluated doses approved by the European Medicines Agency at the time the trial started. A total of 674 children < 18 years were enrolled; 282 children started dolutegravir as first-line therapy and 392

started dolutegravir as second-line therapy (*11*). Nested pharmacokinetic substudies within ODYSSEY evaluated simplified paediatric dosing aligned with WHO-recommended weight bands. Pharmacokinetic data are available from a cohort of children weighing > 25 kg who switched to dolutegravir 50 mg film-coated tablets (*12*). Data from another ODYSSEY cohort reported on children weighing 20–< 25 kg who received either dolutegravir 50 mg film-coated tablets or 30 mg of dolutegravir administered as six 5 mg dispersible tablets. Both of these doses achieved area under the curve (AUC) and C_{max} values that were higher than adult pharmacokinetic reference values, but are still acceptable, and both doses achieved C_{trough} values that were similar to adult reference values, as was weight-band dosing for infants and children under 20 kg (*13*, *14*).

Dolutegravir dosing in the ODYSSEY study for weight bands under 20 kg was slightly different from that in P1093, mainly because P1093 was originally designed to dose by age rather than by weight band. Both studies contributed pharmacokinetic data to the regulatory submissions for the innovator's dispersible tablet (Tivicay PD®, dolutegravir 5 mg tablets for oral suspension, ViiV Healthcare). Combined pharmacokinetic data from P1093 and ODYSSEY across all age and weight cohorts form the basis for the current FDA and WHO treatment recommendations and are summarized in Table 2 of the prescribing information on Tivicay and Tivicay PD (*8*). In addition, modelling and simulation studies that included uridine diphosphate glucuronosyltransferase 1-1 (UGT1A1) maturation in infants was used to support the dose of dolutegravir down to 4 weeks of age and 3 kg.

In adult clinical studies to date, dolutegravir-based regimens were either non-inferior or superior in efficacy to comparator regimens containing other integrase inhibitors, boosted protease inhibitors and non-nucleoside reverse-transcriptase inhibitors regardless of patient population. No comparative paediatric trials are available but both the WHO working groups and multiple regulatory agencies (including the FDA and the European Medicines Agency) endorse the concept of extrapolating efficacy from well designed, adequately powered adult trials on the basis of similar pharmacokinetic profiles and supplementary safety data.

Summary of evidence: harms (from the application)

The harms associated with dolutegravir were reviewed and summarized at the time of the previous EML and EMLc applications and the associated evidence is available in the technical reports of the meetings (*1*, *2*).

The FDA clinical review of the data submitted to support registration of dolutegravir dispersible tablets describes the safety data available from P1093 up to 48 weeks of dosing. In P1093, 13 participants (17%) experienced adverse reactions attributed to dolutegravir and all were assessed as Grade 1 or Grade 2 (mild or moderate). Adverse drug reactions reported in more than one study

participant were: decreased blood bicarbonate (three participants), decreased haemoglobin (two participants), decreased neutrophil count (four participants), and immune reconstitution inflammatory syndrome (two participants). In data evaluated by the FDA in support of the dispersible tablet registration, new adverse events occurred in seven participants (7%) in the ODYSSEY safety population (n = 97) through week 24. The only adverse event reported in more than one participant was anaemia in three participants (3%). The following adverse events occurred in only one participant each: neutropenia, diarrhoea, hepatitis A, lower respiratory tract infection, measles, cryptococcal meningitis, otitis media, pneumonia, dehydration and malnutrition. None of these adverse events were thought to be related to the study medicine by the investigators (*15*). Overall, the safety profile in P1093 participants was comparable to that observed in adults and both formulations were well tolerated by paediatric patients (*8*–*10*). Long-term safety assessments in the ODYSSEY trial are ongoing and final data up to 96 weeks of dosing are expected later in 2021.

Additional evidence (not in the application)

Not applicable.

WHO guidelines

WHO's 2018 updated recommendations on first-line and second-line antiretroviral regimens for treatment of HIV in infants and children include dolutegravir as a preferred drug for first-line therapy in all ages for which dosing recommendations and a formulation are available (*16*). This recommendation predated the availability of a child-friendly dolutegravir formulation but can now be widely applied across ages and weight bands. Dolutegravir should be given together with two nucleoside reverse-transcriptase inhibitors appropriate for paediatric patients (abacavir plus lamivudine, or zidovudine plus lamivudine). In addition, the 2018 WHO guidelines also recommend dolutegravir in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone as the preferred second-line regimen for children with approved dolutegravir dosing for whom non-dolutegravir-based regimens are failing.

Dosing recommendations for dolutegravir 10 mg scored dispersible tablets for infants and children 4 weeks and older and weighing ≥ 3 kg are:

- 3 kg to < 6 kg, 5 mg once daily (half a tablet)
- 6 kg to < 10 kg, 15 mg once daily (1.5 tablets)
- 10 kg to < 14 kg, 20 mg once daily (2 tablets)
- 14 kg to < 20 kg, 25 mg once daily (2.5 tablets)
- ≥ 20 kg, 30 mg once daily (3 tablets).

Alternatively, paediatric patients weighing ≥ 20 kg may follow the dosing recommendations using dolutegravir 50 mg tablets (50 mg once daily).

Because the dispersible tablets are more bioavailable than the previously approved film-coated tablets, 30 mg given as 3 × 10 mg dispersible tablets provides similar drug exposure as one 50 mg film-coated tablet given once daily (adult dose).

HIV infection can be diagnosed with relatively simple, point-of-care, rapid testing kits or in clinic or hospital laboratories. WHO recommends treatment for all patients diagnosed with HIV infection regardless of age, clinical stage or laboratory parameters. While receiving dolutegravir as part of an antiretroviral therapy regimen, patients should be monitored for treatment failure according to national guidelines. However, specialized testing is not required for patient diagnosis or management while receiving dolutegravir-based therapy. HIV requires life-long treatment.

Costs/cost–effectiveness

No known cost–effectiveness studies have been conducted for dolutegravir dispersible scored tablets.

Availability

At the time of the recent paediatric dispersible tablet review, the FDA revised dosing recommendations for the 50 mg tablets to allow use in children down to 20 kg. Dolutegravir 5 mg tablets for oral suspension (Tivicay PD, ViiV Healthcare) are approved for infants and children 4 weeks of age and older and weighing 3 kg or more in the United States and the European Union. Registration of tablets for oral suspension (also called dispersible tablets) produced by ViiV Healthcare is in progress in additional countries. Licence agreements for dolutegravir have been made available by innovator companies through the Medicines Patent Pool. In addition, ViiV Healthcare, Clinton Health Access Initiative, Inc. (CHAI), Mylan (now Viatris, Inc.) and Macleods Pharmaceuticals Ltd have formed a novel partnership to accelerate development of an optimized paediatric formulation of dolutegravir and bring it to market in low- and middle-income countries (*17*).

The optimal formulation to provide appropriate dosing for all age and weight bands was identified by the WHO-sponsored Paediatric Antiretroviral Drug Optimization (PADO) working group as a dolutegravir 10 mg scored dispersible tablet (*18*). This formulation was added subsequently to the WHO prequalification expression of interest list. The FDA granted tentative approval of the first generic version of dolutegravir 10 mg scored dispersible tablets (Mylan, Hyderabad) on 19 November 2020. By virtue of the FDA tentative approval, Mylan's dispersible tablets will be cross-listed on the WHO List

of Prequalified Medicinal Products. Another supplier's product (Macleods Pharmaceuticals, Mumbai) is currently under review by both the FDA and the WHO prequalification team.

Other considerations

The FDA approved label for Tivicay branded dolutegravir 50 mg tablets and 5 mg dispersible tablets states that the two dosage forms are not bioequivalent. The relative bioavailability of Tivicay PD is about 1.6-fold higher than Tivicay; therefore, the two dosage forms are not interchangeable on a milligram-to-milligram basis.

Committee recommendations

The Expert Committee recognized that age-appropriate, child-friendly formulations of antiretroviral medicines, when available and quality-assured, are essential to meet the needs of paediatric patients with HIV.

The Committee noted evidence that dolutegravir-based regimens show superiority over NNRTI plus protease inhibitor regimens in paediatric patients and that the dolutegravir-based regimens have been recommended in WHO guidelines as the preferred first-line therapy in infants and children aged 4 weeks and older, for which dosing recommendations and age-appropriate formulations are available.

The Committee therefore recommended the inclusion of the new formulation of dolutegravir 10 mg dispersible tablets to the core list of the EMLc for the treatment of children 4 weeks of age and older and weighing at least 3 kg.

The Committee noted however that the 10 mg dispersible tablet formulation and the 50 mg film-coated tablet formulation of dolutegravir have not been shown to be bioequivalent and should not be used interchangeably in patients on a milligram-to-milligram basis.

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6.4.2.5 *Fixed-dose combinations of antiretroviral medicines*

Abacavir + lamivudine + lopinavir/ritonavir – new formulation – EMLc

Abacavir + lamivudine + lopinavir + ritonavir	**ATC Code: to be assigned**

Proposal

Inclusion of a single-pill combination formulation of abacavir, lamivudine and lopinavir/ritonavir to the core list of the EMLc for treatment of HIV infection in children.

Applicant

Irene Mukui, Janice Lee, François Bompart, Isabelle Andrieux-Meyer, Mariana Diallo; Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland

WHO technical department

Global HIV, Hepatitis and STIs Programmes

EML/EMLc

EMLc

Section

6.4.2.5 Fixed-dose combinations of antiretroviral medicines

Dose form(s) & strength(s)

Oral granules in capsule: 30 mg + 15 mg + 40 mg + 10 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

This formulation had not previously been considered for inclusion on the EMLc. The component medicines are all included on the EMLc in paediatric-friendly formulations.

Public health relevance (burden of disease)

HIV infection among children is still a significant problem in developing countries, despite the global progress made in HIV prevention and AIDS

treatment. Of the estimated 1.8 million children younger than 15 years living with HIV, 88% live in sub-Saharan Africa and only 53% of the total were receiving antiretroviral therapy by the end of 2019 (*1*). Many factors contribute to the low treatment coverage for children living with HIV, including challenges unique to children's medicines, diagnosis, case-finding and linkage, and their retention in care (2). Diagnosis of HIV in infants (both early diagnosis and final diagnosis after 18 months) remains poor in many countries, which impedes scaling up treatment for children, especially those younger than 18 months. Even among children who do get onto treatment, retention among children is hindered for many reasons, such as the lack of and sustainable supply of appropriate formulations (*3*), maintaining a market share for available paediatric formulations and ensuring access in each country (*4*).

Globally in 2019, an estimated 95 000 children younger than 15 years died of AIDS-related causes (*1*). Without HIV treatment, 50% of infants infected with HIV during or around the time of birth will die by the age of 2 years (*4*). Many studies have shown that early initiation of antiretroviral therapy in HIV-infected children is associated with clinical and survival benefits (*5*–*11*).

Summary of evidence: benefits (from the application)

The phase I/II LOLIPOP study is assessing the pharmacokinetics, safety and acceptability of the fixed-dose combination formulation of abacavir + lamivudine + lopinavir/ritonavir in children living with HIV (*12*). The 4-in-1 combination (test formulation) was compared with abacavir 60 mg + lamivudine 30 mg (dispersible tablets) + lopinavir/ritonavir 40 mg/10 mg (pellets) (reference formulation) in children infected with HIV and weighing 3–25 kg (inclusive) in Uganda.

Study drugs were dosed by WHO weight bands: 3–5.9 kg (weight band 1), 6–9.9 kg (weight band 2), 10–13.9 kg (weight band 3) or 14–19.9 kg (weight band 4). Children in weight bands 2 to 4 were randomly assigned (1:1) by weight band to the reference formulation followed by the test formulation for 21 days each (RT) or to the test formulation followed by reference formulation for 21 days each (TR). Children in weight band 1 only received the test formulation for 21 days. Intensive pharmacokinetic sampling was done after 21 days of treatment with each formulation.

Safety was assessed during the whole study period and efficacy at the end of the study. Children's caregivers completed an acceptability questionnaire on the 4-in-1 treatment after 21 days. The application reported interim data on the first 33 enrolled children. Of these, four children were in weight band 1. Of the 29 children in weight bands 2–4, 15 were assigned to RT and 14 were assigned to TR. All children were already on lopinavir/ritonavir therapy and 76% had been on antiretroviral therapy for 6 months or more at the time of enrolment. Most children (88%) had a viral load < 400 copies/mL at baseline.

Datasets were available for 31 children.

Interim efficacy results showed that the proportion of children with viral load < 400 copies/mL increased from 88% (29/33) at baseline to 97% (30/31) at the end of the study. The proportion with viral load < 50 copies/mL increased from 48% (16/33) to 65% (20/31), when missing data were excluded. The median change in CD4 cell count was +130 (interquartile range (IQR) –398 to +527) and, on average, there was no change in CD4% (IQR –3% to +2%) between baseline and end of the study.

Interim pharmacokinetic results showed that with the 4-in-1 formulation, the geometric means for area under the curve 0–12 ($AUC_{0\text{-}12}$) for abacavir, lamivudine, and lopinavir/ritonavir were 5479 ng.h/mL, 6059 ng.h/mL and 88 398 ng.h/mL, respectively. Geometric means for maximum concentration (C_{max}) were 1754 ng/mL, 1125 ng/mL and 10 103 ng/mL, respectively. Two children in weight band 1 (with severe wasting secondary to failure to thrive) had lopinavir 12-hour postdose concentration (C_{12}) less than 1000 ng/mL; one remained virally suppressed and one became virally suppressed at the end of the study.

Pharmacokinetic results for abacavir showed overlapping exposure curves between the test and reference formulations. The geometric mean ratio was 94% for AUC and 76% for C_{max}. The bioequivalence criteria were met for abacavir AUC.

Pharmacokinetic results for lamivudine showed the geometric mean ratio was 82% for AUC and 69% for C_{max}. Neither AUC nor C_{max} met bioequivalence criteria, but were comparable to historical exposures in adults and children.

Pharmacokinetic results for lopinavir showed that the geometric mean ratio for AUC was 12% lower with the test than the reference formulation, with the lower limit of the 90% confidence interval outside the bioequivalence range. For C_{max}, the geometric mean ratio was 17% lower with the test formulation. Lopinavir absorption was slower with the test formulation than the reference formulation. Overall, lopinavir exposure was comparable to historical data in adults. Exposure to lopinavir by formulation and weight band showed close to the expected ranges observed in adults for weight bands 2–4. No conclusions could be drawn at this time for weight band 1 because of the small and heterogeneous population in this group.

Pharmacokinetic results for ritonavir showed the geometric mean ratio was 87% for AUC and 82% for C_{max}.

Summary of evidence: harms (from the application)

The safety of abacavir, lamivudine, and lopinavir/ritonavir as individual medicines has been previously evaluated.

From the interim results of the LOLIPOP study, 101 treatment-emergent adverse events were reported, most of which (96%) were mild, and none led to

treatment discontinuation. Treatment-emergent adverse events occurred more frequently with the test formulation than the reference formulation (74% versus 56%, respectively) and the same was true for treatment-related adverse events (42% versus 30%).

In terms of acceptability, among 31 caregivers interviewed, 97% reported that administering the 4-in-1 formulation was easy or very easy, and 71% reported that the child had no difficulty swallowing it.

Additional evidence (not in the application)

Not applicable

WHO guidelines

In 2013, WHO guidelines recommended the use of lopinavir/ritonavir-based regimens in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) as first-line antiretroviral therapy for all children younger than 3 years infected with HIV, regardless of exposure to non-nucleoside reverse transcriptase inhibitors (*13*).

The 2018 WHO guidelines on treating and preventing HIV infection recommended a dolutegravir-based regimen in combination with abacavir and lamivudine as the preferred first-line regimen for children for whom approved dolutegravir dosing is available (*14*). In the absence of appropriate dolutegravir formulations and dosing for infants and young children, abacavir and lamivudine in combination with lopinavir/ritonavir is considered an acceptable alternative given the superiority of lopinavir/ritonavir over regimens based on non-nucleoside reverse-transcriptase inhibitors (*15*). As of 2020, implementation of dolutegravir-based regimens in children has only been feasible for children weighing ≥ 20 kg in whom dolutegravir 50 mg tablets can be used, while children weighing < 20 kg continue to use lopinavir/ritonavir-based regimens (*15*). Abacavir + lamivudine in combination with lopinavir/ritonavir is still an important alternative regimen for use as first-line treatment for infants and young children (*14*).

Costs/cost–effectiveness

The application stated that the proposed fixed-dose combination formulation was not yet marketed, nor was the final price available. The manufacturer, Cipla, has announced an ex-factory price of US$ 15 per pack of 120 capsules. This corresponds to a price per patient per year of US$ 360 for children in weight band 3 (10–13.9 kg). In comparison, the price per patient per year for the component medicines as separate formulations in this weight band is US$ 520.

Availability

This formulation does not yet have regulatory approval anywhere in the world. It is currently under review by regulatory authorities in the Democratic Republic

of the Congo, Kenya, Malawi, Mozambique, Rwanda, South Africa, Tanzania, Uganda, United States of America (USA), Zambia and Zimbabwe.

Other considerations

Among people with the HLA-B*5701 allele, the use of abacavir can cause fatal hypersensitivity and screening for this allele before starting therapy with abacavir is recommended in Australia, Europe and USA (*16*). However, data on the prevalence of the HLA-B*5701 allele and usefulness of testing for it among black African children, who comprise most children living with HIV globally, show a low prevalence of the allele (*17*, *18*). Furthermore, the prevalence of adverse events related to abacavir is low, and adverse events occur early in treatment and can be managed. WHO therefore recommends the use of abacavir-based regimens in first- and second-line antiretroviral regimens without the need for testing (*19*).

Committee recommendations

The Expert Committee recognized that age-appropriate, fixed-dose combination formulations of antiretrovirals, when available and quality-assured, are preferred over multiple single-agent formulations to improve treatment adherence and reduce the tablet burden for patients.

The Committee noted that dolutegravir, in combination with abacavir and lamivudine, is recommended as the preferred first-line treatment regimen for children with HIV infection in current WHO guidelines, but that abacavir and lamivudine, in combination with lopinavir/ritonavir is an acceptable alternative when dolutegravir-based treatment is not available or appropriate.

However, the Committee noted that pharmacokinetic results from the LOLIPOP study indicate that the proposed fixed-dose combination did not meet the criteria for bioequivalence when compared with the reference products, which are currently included on the EMLc. In addition, the Committee noted that the proposed formulation has not yet received regulatory approval from the US Food and Drug Administration.

Therefore, the Committee did not recommend inclusion of the fixed-dose combination formulation of abacavir + lamivudine + lopinavir/ritonavir on the EMLc.

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6.4.3 Other antivirals

Oseltamivir – deletion – EML and EMLc

Oseltamivir **ATC Code: J05AH02**

Proposal

Deletion of oseltamivir oral powder 12 mg/mL formulation from the complementary list of the EML and EMLc.

Applicant

F. Hoffman-La Roche Ltd, Basel, Switzerland

WHO technical department

Department of Global Infectious Hazard Preparedness

EML/EMLc

EML and EMLc

Section

6.4.3 Other antivirals

Dose form(s) & strength(s)

Oral powder: 12 mg/mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Oseltamivir (capsules 30 mg, 45 mg and 75 mg; oral powder 12 mg/mL) was added to the core list of the EML and EMLc in 2011 for treatment of influenza following the 2009 H1N1 influenza outbreak which was classified at the time as a public health emergency (*1*). In 2017, the Expert Committee reviewed additional evidence for oseltamivir in seasonal and pandemic influenza which indicated that the beneficial effect of oseltamivir on relevant outcomes of hospital admissions and mortality was lower than previously estimated. The Expert Committee therefore recommended oseltamivir be transferred from the core to the complementary list, and its use be limited to patients with severe illness due

to confirmed or suspected influenza virus infection in critically ill hospitalized patients (*2*).

Public health relevance (burden of disease)

Influenza serotypes A and B infect humans and are responsible for an acute febrile infection of the respiratory tract characterized by the sudden onset of cough, fever, headache, malaise and myalgia. Illnesses range from mild to severe and even death. Hospitalization and death occur mainly among high-risk groups. Influenza is a seasonal illness, with epidemic infections occurring annually during cooler months. Annual influenza epidemics are thought to result in between 3 and 5 million cases of severe illness and between 290 000 and 650 000 respiratory deaths worldwide (*3*).

In industrialized countries, most deaths associated with influenza occur among people aged 65 years or older (*4*). It is estimated that 99% of deaths in children under 5 years with influenza-related lower respiratory tract infections occur in developing countries (*5*).

Summary of evidence: benefits (from the application)

Evidence of the clinical efficacy of oseltamivir was previously reviewed by the Expert Committee in 2011 (*1*), 2013 (*6*) and 2017 (*2*).

Summary of evidence: harms (from the application)

Evidence for the safety of oseltamivir was previously reviewed by the Expert Committee in 2011 (*1*), 2013 (*6*) and 2017 (*2*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

Not applicable

Costs/cost–effectiveness

Not applicable

Availability

Roche ceased to manufacture and supply its brand of this formulation (Tamiflu®) in August 2016, with the last commercial supply in February 2017. Global deregistration for Tamiflu 12 mg/mL oral powder is ongoing.

The approved labelling for Tamiflu® capsules includes instructions for pharmacists on compounding a 6 mg/mL oral suspension of oseltamivir using the contents of the 30 mg, 45 mg or 75 mg capsule formulations (*7*). The

application stated that generic brands of oseltamivir capsule formulations are widely available in many countries from which oral suspension formulation may be compounded.

Other considerations

Oseltamivir capsules 30 mg, 45 mg and 75 mg are still included on the Model Lists.

Committee recommendations

The Expert Committee recommended the deletion of oseltamivir powder for oral liquid 12 mg/mL from the complementary list of the EML and EMLc noting that this formulation has been discontinued by the manufacturer and is no longer marketed.

The Committee noted that the capsule formulations of oseltamivir can be manipulated for the preparation of an oral suspension, providing an alternative for patients, particularly young children, who are unable to take a solid dosage form. However, the Committee also recognized the importance of having age-appropriate formulations for children that do not need to be compounded or manipulated. The Committee noted the market availability of a 6 mg/mL oseltamivir powder for oral liquid formulation, and requested that the manufacturer be asked to clarify the status of this particular product.

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6.4.4 Antihepatitis medicines

6.4.4.2 *Medicine for Hepatitis C*

Glecaprevir + pibrentasvir – addition – EMLc

Glecaprevir + pibrentasvir **ATC Code: J05AP57**

Proposal

Addition of glecaprevir + pibrentasvir fixed-dose combination on the core list of the EMLc for the treatment of chronic hepatitis C virus infection (all genotypes) in paediatric patients.

Applicant

Fondazione Penta ONLUS, Padua, Italy

WHO technical department

Global Hepatitis Programme

EML/EMLc

EMLc

Section

6.4.4.2.1 Pan-genotypic direct-acting antiviral combinations

Dose form(s) & strength(s)

Tablet: 100 mg + 40 mg
Granules: 50 mg + 20 mg in sachet

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The fixed-dose combination of glecaprevir + pibrentasvir was added to the core list of the EML in 2019 for the treatment of adult patients with chronic hepatitis C virus (HCV) infection, based on evidence of pan-genotypic effectiveness and an acceptable safety profile. The Expert Committee noted that this combination is one of three pan-genotypic combinations recommended in the current WHO guidelines for treatment of hepatitis C and is suitable for use in patients with or without compensated cirrhosis (*1*).

Public health relevance (burden of disease)

Chronic HCV infection remains a main cause of liver disease globally, with an estimated 71 million people living with chronic HCV overall as of 2015 and an estimated 1.75 million new cases a year (*2*). Previously, interferon-based therapy was long and difficult to tolerate, had a low success rate, and required extensive clinical and laboratory monitoring during treatment. The introduction of multiple all-oral, direct-acting antiviral treatments has led to rates of sustained virological response greater than 90% with treatment courses of 12 weeks and greatly improved safety. With these improved characteristics acknowledged, in 2016, the World Health Assembly adopted targets for the elimination of chronic HCV as a public health threat by 2030 (*3*). Treatment of chronic HCV in adults in low- and middle-income countries has been scaled up as availability of direct-acting antiviral treatments has increased.

Little emphasis has been placed on chronic HCV in children, and the prevalence, epidemiology and natural history of infection are less well understood in children than in adults. A recently published modelling exercise estimated that 3.26 million children are living with chronic HCV infection, and 20 countries account for 80% of all cases in patients aged 0–18 years. Countries with the highest number of children with chronic HCV include China, Egypt, India, Nigeria and Pakistan (*4*). The main mode of acquisition of HCV infection in children is mother-to-child transmission, although older children and adolescents may become infected through unsafe injection practices or poor infection control practices. About 5% of infants born to mothers with HCV infection will acquire the infection, up to 10% if the mother is co-infected with HIV. The risk of transmission increases with increasing levels of maternal HCV RNA (*5*).

Most children with liver disease are asymptomatic or minimally symptomatic and cirrhosis and hepatocellular carcinoma are rare in this age group, which allows treatment to be deferred in younger children according to previous treatment guidelines. As noted in a recent publication, including children and adolescents in national HCV surveillance, testing and treatment programmes can eventually help achieve the goal of HCV elimination (*6*).

Summary of evidence: benefits (from the application)

The DORA study is a paediatric trial of glecaprevir + pibrentasvir in patients aged 3 to < 18 years being conducted by Abbvie. To date, the registration study has enrolled children with chronic HCV infection at sites in Belgium, Canada, Germany, Japan, Puerto Rico, Russian Federation, Spain, United Kingdom of Great Britain and Northern Ireland and United States of America across four age groups: 12–17 years (n = 47), 9–11 years (n = 29), 6–8 years (n = 27) and 3–5 years (n = 24) (*7*, *8*).

Results from DORA part 1 were submitted for regulatory review and led to the approval of glecaprevir + pibrentasvir for use in children 12 years of age and older or weighing at least 45 kg. Across this age group, about 79% were infected with genotype 1 HCV, 6% with genotype 2, 8% with genotype 3 and 6% with genotype 4. Adolescents received 300 mg/120 mg (glecaprevir/pibrentasvir) once daily for 8 weeks or for 16 weeks (HCV genotype 3, treatment experienced), after which they were monitored for 12 weeks to assess treatment response. Overall, 100% of the study participants achieved sustained virological response (95% CI 92.4 to 100.0). The study showed that the plasma concentrations of glecaprevir and pibrentasvir in the participants were comparable to those observed in adults receiving the recommended dose (*7*).

DORA part 2 was a phase II/III, non-randomized, open-label, multinational study that evaluated the efficacy, safety and pharmacokinetics of a glecaprevir + pibrentasvir paediatric granules formulation in children aged ≥ 3 to < 12 years with HCV infection (genotype 1–6) (*8*). Participants were divided into three age groups. In each group, participants were first enrolled in parallel into an intense pharmacokinetics portion to characterize the pharmacokinetics and safety in each age group, followed by a non-intense pharmacokinetics safety and efficacy portion. Treatment durations were based on adult treatment recommendations in accordance with local prescribing labels. Data for the three age groups in DORA part 2 are summarized in Table 3.

Table 3
Characteristics of the participant groups in the DORA part 2 trial

Characteristic	Age group (years)			Total
	9–11	6–8	3–5	
Sample size (*n*)	29	27	24	80
SVR12, no. (%)	27 (93)	27 (100)	23 (96)	77 (96)
Relapse, no.	1[a]	0	0	1
Treatment discontinuation, no.	1[b]	0	1[c]	2
Dose glecaprevir/ pibrentasvir (mg)	250/100	200/80	150/60	NA

SVR12: sustained virological response 12 weeks after the end of the treatment; NA: not applicable.
[a] One participant relapsed after treatment in week 4.
[b] One participant prematurely discontinued the trial due to a drug-related rash.
[c] One participant refused to swallow the granule formulation and prematurely discontinued the trial after having received a partial dose on Day 1. This participant did not receive subsequent doses.
Jonas MM, at al., 2020 (*8*).

In summary, high rates of sustained virological response 12 weeks post-treatment were seen in children aged ≥ 3 to < 12 years with chronic HCV infection. No virological failures were seen on the dose ratio of 50 mg/20 mg.

Summary of evidence: harms (from the application)

To date, the number of children treated with glecaprevir + pibrentasvir is very small.

Direct-acting antiviral treatments in general, and glecaprevir + pibrentasvir in particular, are well tolerated and serious adverse events are uncommon. Glecaprevir + pibrentasvir was generally well tolerated in the paediatric registration trial (*7*, *8*).

In the phase II and phase III adult registration trials of glecaprevir + pibrentasvir, the most commonly observed adverse reactions (all severity grades) in participants receiving 8 weeks of glecaprevir + pibrentasvir treatment were headache and fatigue. Less than 0.1% of participants treated with glecaprevir + pibrentasvir experienced serious adverse reactions, e.g. transient ischaemic attack (*9*).

The most common adverse events among the 47 adolescents in the older DORA group included nasopharyngitis (26%), upper respiratory tract infection (19%), headache (17%), fatigue (11%), oropharyngeal pain (11%) and pyrexia (11%). There was no grade 3 or higher aminotransferase or bilirubin elevations, no liver-related toxicities and no cases of drug-induced liver injury (*7*). In the younger DORA groups, adverse events were mild and no serious adverse events occurred. One adverse event led to treatment discontinuation. The most common adverse events observed in the 80 participants included headache (14%), vomiting (14%) and diarrhoea (10%) (*8*).

No comparative safety data with other direct-acting antiviral regimens in paediatric patients are available. A systematic review of 39 studies that evaluated the efficacy and safety of direct-acting antiviral treatments in 1796 children and adolescents reported all regimens studied, including glecaprevir + velpatasvir, were well tolerated (*10*).

No specific safety issues associated with glecaprevir + pibrentasvir are known that would be expected to pose a different risk in an international health setting. No special laboratory monitoring is required, so no potential harm is likely to patients if this function is not available in a clinic setting in low and middle income countries.

Additional evidence (not in the application)

Pharmacokinetic characteristics of the 50 mg + 20 mg paediatric formulation of glecaprevir + pibrentasvir were evaluated in the three age groups in part 2 of the DORA study (*11*). After pharmacokinetic samples were analysed, doses

were adjusted from an initial dose ratio of 40 mg + 15 mg to 50 mg + 20 mg to achieve therapeutic exposures similar to adults. The final paediatric weight-based dosages are shown in Table 4.

Table 4
Final paediatric dosages of glecaprevir + pibrentasvir based on weight

Age group/weight band	Dose (glecaprevir + pibrentasvir)
9 to < 12 years/30 kg to < 45 kg	250 mg + 100 mg
6 to < 9 years/20 kg to < 30 kg	200 mg + 80 mg
3 to < 6 years/12 kg to < 20 kg	150 mg + 60 mg

The pharmacokinetic exposures of glecaprevir and pibrentasvir in paediatric patients were comparable to exposures in adults and adolescents, and the final doses used achieved target exposure levels.

WHO guidelines

Glecaprevir + pibrentasvir is one of the three recommended pan-genotypic regimens for adults in the 2018 *WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* (*2*).

Glecaprevir + pibrentasvir is expected to be added as a treatment for adolescents and children with chronic HCV infection in the planned update to the guideline chapter on treatment in adolescents and children. The regimen is expected be recommended as therapy for paediatric patients for whom dosing recommendations and an appropriate formulation are available. This update will be published in mid-2021 as a rapid communication policy brief, and the updated chapter on treatment of adolescents and children will be included in the overall WHO consolidated guidelines on testing, care and treatment of viral hepatitis to be published at the end of 2021.

Costs/cost–effectiveness

A recent study surveyed the current prices of originator direct-acting antiviral medicines in 50 countries (*12*). The cost of a standard adult course of glecaprevir + pibrentasvir compared well with that of other direct-acting antiviral combinations: median originator prices per standard course were US$ 41 000 for sofosbuvir, US$ 27 000 for daclatasvir, US$ 34 000 for sofosbuvir + velpatasvir and US$ 31 000 for glecaprevir + pibrentasvir. The variability of pricing across countries was high. Generic prices estimated based on costs of active pharmaceutical ingredients (API), excipients, manufacturing of finished pharmaceutical product, taxes and a 10% profit margin were approximately

1000 times lower than the originator prices cited above: US$ 58 for sofosbuvir + velpatasvir and US$ 31 for sofosbuvir + daclatasvir. The API cost data for glecaprevir + pibrentasvir were insufficient to calculate an estimated cost of a generic formulation, but the data above indicate that the price of a generically produced product could be comparable to that of generically produced alternative fixed dose combinations.

Availability

Glecaprevir + pibrentasvir tablets and granules are manufactured by AbbVie.

AbbVie and the Medicines Patent Pool have entered into a royalty-free licensing agreement to accelerate access to glecaprevir + pibrentasvir in 99 low- and middle-income countries and territories at affordable prices, enabling treatment scale-up with glecaprevir + pibrentasvir. Through this agreement, AbbVie will grant WHO prequalified generic manufacturers to license, manufacture and supply generic versions of glecaprevir + pibrentasvir, while maintaining the highest quality and production standards.

Other considerations

Not applicable

Committee recommendations

The Expert Committee recommended the addition of the fixed-dose combination of glecaprevir + pibrentasvir to the core list of the EMLc for the treatment of children aged 3 to 12 years with chronic HCV infection, based on evidence of pan-genotypic effectiveness and an acceptable safety profile.

The Committee noted that the results from the DORA trial demonstrated high rates of virological response in children and adolescents, comparable with those observed in adults. The Committee therefore also recommended that listing of glecaprevir + pibrentasvir on the EML be extended to include adolescents.

The Committee also noted the planned inclusion of glecaprevir + pibrentasvir as one of the recommended regimens for children in the updated WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection*, and the licensing agreements in place between the manufacturer and the Medicines Patent Pool, which aims to facilitate affordable access to glecaprevir + pibrentasvir in low- and middle-income countries.

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Daclatasvir and sofosbuvir – addition – EMLc

Daclatasvir	**ATC Code: J05AP07**
Daclatasvir + sofosbuvir	**ATC Code: to be assigned**
Sofosbuvir	**ATC Code: J05AP08**

Proposal

Addition of sofosbuvir and daclatasvir, as both the single medicines and as a fixed-dose combination, to the core list of the EMLc for the treatment of chronic hepatitis C virus infection (all genotypes) in paediatric patients.

Applicant

Clinton Health Access Initiative, Inc., United States of America

WHO technical department

Global Hepatitis Programme

EML/EMLc

EMLc

Section

6.4.4.2.1 Pan-genotypic direct-acting antiviral combinations

Dose form(s) & strength(s)

Daclatasvir: tablet 30 mg; 60 mg
Daclatasvir + sofosbuvir: tablet 60 mg + 400 mg
Sofosbuvir: tablet 200 mg; 400 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Sofosbuvir 400 mg tablets and daclatasvir 30 mg and 60 mg tablets were added to the core list of the EML in 2015 for the treatment of chronic hepatitis C virus (HCV) infection in adults based on evidence of significantly improved sustained virological response rates and better side-effect profiles compared with interferon-based regimens (*1*).

Public health relevance (burden of disease)

Chronic HCV infection remains a main cause of liver disease globally, with an estimated 71 million people living with chronic HCV overall as of 2015 and an estimated 1.75 million new cases a year (*2*). Previously, interferon-based therapy was long and difficult to tolerate, had a low success rate, and required extensive clinical and laboratory monitoring during treatment. The introduction of multiple all-oral, direct-acting antiviral regimens has led to sustained virological response rates greater than 90% with treatment courses of 12 weeks and greatly improved safety. With these improved characteristics acknowledged, in 2016, the World Health Assembly adopted targets for the elimination of chronic HCV as a public health threat by 2030 (*3*). Treatment of chronic HCV in adults in low- and middle-income countries has been scaled up as availability of direct-acting antiviral treatments has increased. Sofosbuvir combined with daclatasvir has become the preferred pan-genotypic direct-acting antiviral regimen in low- and middle-income countries because low-cost generic products are available.

Little emphasis has been placed on chronic HCV in children and the prevalence, epidemiology and natural history of infection are less well understood in children than in adults. A recently-published modelling exercise, estimated that 3.26 million children are living with chronic HCV infection, and 20 countries account for 80% of all cases in patients aged 0–18 years. Countries with the highest number of children with chronic HCV include China, Egypt, India, Nigeria and Pakistan (*4*). The main mode of acquisition of HCV infection in children is mother-to-child transmission, although older children and adolescents may become infected through unsafe injection practices or poor infection control practices. About 5% of infants born to mothers with HCV infection will acquire the infection, up to 10% if the mother is co-infected with HIV. The risk of transmission increases with increasing levels of maternal HCV RNA (*5*). In one Egyptian study of children aged 8 to 18 years, 77.5% had a family member infected with HCV and 62.5% had an HCV-infected mother (*6*).

Most children with liver disease are asymptomatic or minimally symptomatic and cirrhosis and hepatocellular carcinoma are rare in this age group, which allows treatment to be deferred in younger children according to previous treatment guidelines. As noted in a recent publication, including children and adolescents in national HCV surveillance, testing, and treatment programmes can eventually help achieve the goal of HCV elimination (*7*).

Summary of evidence: benefits (from the application)

A systematic review and meta-analysis of 39 studies (1796 patients) evaluated the efficacy and safety of direct-acting antiviral medicines in children and adolescents with chronic HCV infection (*8*). Regimens containing sofosbuvir were given to 1674 patients, including 206 who received sofosbuvir plus daclatasvir, with a

small number of these also receiving ribavirin. Sustained virological response ranged from 96.7% to 100% in the 11 studies reporting results for sofosbuvir plus daclatasvir included in the systematic review.

Several small observational studies in patients younger than 18 years evaluating sofosbuvir plus daclatasvir have also been done. A prospective, observational study of Indian children aged 10 to 18 years with thalassaemia major evaluated the safety and efficacy of treatment with sofosbuvir 400 mg plus daclatasvir 60 mg for 12 weeks (9). All the children in the study (n = 10) were treatment naive, did not have cirrhosis and had genotype 3 HCV. They all responded well to therapy with reported improvement in liver aminotransferases and the sustained virological response was 100%.

A study of adolescents aged 12 to 18 years infected with HCV in India assessed a decentralized public health approach to management that included optional genotype testing for patients without cirrhosis and the safety of treatment with direct-acting antivirals (*10*). A total of 45 patients were treated with sofosbuvir and daclatasvir, 43 without cirrhosis and two with cirrhosis. Both the patients with cirrhosis (who also received weight-based ribavirin and a longer course of treatment) and 42 (97.7%) patients without cirrhosis showed a sustained virological response.

A study in Egypt reported on the treatment of 40 treatment-naïve children aged 8 to 18 years with HCV infection, genotype 4 or mixed genotypes 4 and 1 (*6*). Children weighing > 45 kg received sofosbuvir 400 mg plus daclatasvir 60 mg and those weighing 17–45 kg received sofosbuvir 200 mg plus daclatasvir 30 mg. Liver aminotransferases normalized in all children by the end of 12 weeks of treatment and 97.5% showed a sustained virological response. The child who failed to achieve a sustained virological response was lost to follow-up but had undetectable HCV RNA at the end of treatment. Another Egyptian study of 17 adolescents with HCV genotype 4 who received sofosbuvir 400 mg plus daclatasvir 60 mg evaluated the pharmacokinetics of daclatasvir (*11*). Weight and serum albumin levels were the main factors influencing pharmacokinetic parameters in this study. These patients had pharmacokinetic profiles comparable to those observed in adults receiving the same dose and had good clinical outcomes.

A modelling and simulation study to identify optimal dosing of sofosbuvir and daclatasvir for children weighing between 14 kg and 35 kg was performed as part of the Global Accelerator for Paediatric Formulations collaboration (*12*). Data from an adolescent pharmacokinetic study were used to estimate pharmacokinetic parameters by weight bands in children between 10 kg and 35 kg receiving either 60 mg or 30 mg of daclatasvir. The simulations showed that the proportion of children with very high daclatasvir exposure increased for children weighing less than 30 kg receiving 60 mg of daclatasvir and for children 10–14 kg receiving 30 mg. It was concluded that daclatasvir 30 mg

daily would be expected to provide exposures comparable to adult values in children weighing 14–35 kg.

In the clinical studies to date, sofosbuvir plus daclatasvir regimens have not been routinely compared with other regimens regardless of the population being studied. In its guidance for industry on developing direct-acting antiviral medicines, the United States Food and Drug Administration (FDA) notes that a development plan containing at least one comparative trial is preferred but non-comparative studies using historical controls may be acceptable. In the ENDURANCE-3 trial conducted as part of the registration package for glecaprevir plus pibrentasvir, sofosbuvir plus daclatasvir compared favourably with glecaprevir plus pibrentasvir in participants with genotype 3 HCV infection, with 97% of participants achieving sustained virological response compared to 95% in the glecaprevir plus pibrentasvir arm with no significant differences in safety profiles (*13*).

Summary of evidence: harms (from the application)

To date, the number of children treated with sofosbuvir plus daclatasvir is small but increasing. As noted in the previous section, the systematic review of direct-acting antiviral medicines identified published studies that included 1674 children receiving regimens of sofosbuvir and 206 who received sofosbuvir plus daclatasvir (*8*). Children without cirrhosis receiving their first treatment with sofosbuvir plus daclatasvir were given a 12-week course. Treatment may be extended in those with cirrhosis and/or ribavirin may be added.

Direct-acting antiviral medicines in general, and sofosbuvir plus daclatasvir in particular, are well-tolerated and serious adverse events are uncommon. Discontinuation of treatment before completion of the 12-week course was not described in the paediatric groups reviewed. Furthermore, patients rarely discontinued follow-up before assessing sustained virological response at 12 weeks after completion of treatment.

The most commonly reported adverse events, occurring in more than 5% of paediatric patients receiving any direct-acting antiviral medicine, included headache (19.9%), fatigue (13.9%), nausea (8.1%) and abdominal pain (7.0%) (*8*).

In the Indian study of 45 children treated with sofosbuvir plus daclatasvir, no serious adverse events, such as anaemia or liver decompensation, and no episodes of headache, diarrhoea or fatigue were reported. Two patients developed transient elevation of liver enzymes which resolved without discontinuing treatment (*10*). Similarly, one of the Egyptian studies noted adverse events were mild and none required treatment discontinuation (*6*). In a prospective study of 30 adolescents with HCV infection receiving sofosbuvir plus daclatasvir, the following mild to moderate adverse events were reported in two to four patients each: nausea, abdominal pain, fatigue, headache and pruritus or skin rash. The authors noted no changes in haemoglobin or any other haematological

abnormalities throughout the study (*14*). A study on the effects of sofosbuvir plus daclatasvir treatment on weight and linear growth in adolescents reported no negative impact on linear growth or weight, unlike that reported with interferon-based therapy. Parental reports of increased appetite with treatment and non-statistically significant weight gain were also noted (*15*).

Few comparative safety studies have compared sofosbuvir plus daclatasvir with other direct-acting antiviral regimens in any age group. In the ENDURANCE-3 trial supporting registration of glecaprevir plus pibrentasvir, no significant differences were found in safety profile with a 1% discontinuation rate due to adverse events in the 12-week glecaprevir plus pibrentasvir arm and 1% in the sofosbuvir plus daclatasvir arm (*13*). The most common adverse reactions reported in the 12-week glecaprevir plus pibrentasvir arm compared with the sofosbuvir plus daclatasvir arm were: headache 17% versus 15%, respectively; fatigue 14% versus 12%; and nausea 12% versus 12%.

Additional evidence (not in the application)

Not applicable

WHO guidelines

Sofosbuvir + daclatasvir is one of the three recommended pan-genotypic regimens for adults in the 2018 *WHO guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* (*2*).

Sofosbuvir + daclatasvir is expected to be added as a treatment for adolescents and children with chronic HCV infection in the planned update to the guideline chapter on treatment in adolescents and children. The regimen is expected be recommended as a first-line therapy for paediatric patients for whom dosing recommendations and an appropriate formulation are available. This update will be published in mid-2021 as a rapid communication policy brief and this recommendation will also be included in the overall WHO consolidated guidelines on testing, care and treatment of viral hepatitis to be published at the end of 2021.

Costs/cost–effectiveness

The median cost of treating children who can receive the adult dose of sofosbuvir plus daclatasvir, as single products or the single-pill combination, ranges from US$ 79 to US$ 120 for a standard 12-week course of treatment according to reference pricing guides (Table 5). The CHAI *Hepatitis C market report* published in May 2020 identified that the actual in-country prices for 12 weeks of WHO-prequalified sofosbuvir plus daclatasvir varies from US$ 60 to US$ 1347 (*16*).

Lack of availability of a low-cost generic version of sofosbuvir 200 mg tablets is likely to result in a higher cost for treating children weighing 14–35 kg compared with adults and adolescents. However, costs for low-dose paediatric sofosbuvir plus daclatasvir will decrease as generic products enter the global market.

Table 5
Cost of treatment of sofosbuvir and daclatasvir for patients weighing 14 kg to 35 kg

Reference price	Sofosbuvir 400 mg + daclatasvir 60 mg		Sofosbuvir 400 mg + daclatasvir 60 mg fixed-dose combination		Sofosbuvir 200 mg + daclatasvir 30 mg	
	Price per 28-tablet pack, US$	Median cost 12-week course, US$	Price per 28-tablet pack, US$	Median cost 12-week course, US$	Price per 28-tablet pack, US$	Median cost 12-week course, US$
Global Fund reference price, first quarter 2020 (*17*)	18.20 (sofosbuvir) 12.99 (daclatasvir)	94.00	26.25	79.00	– 10.00 (daclatasvir)	–
MSF access price, fourth quarter 2017 (*18*)	–	120.00	–	–	–	–
UNDP health procurement mechanism, first quarter 2020 (*16*)	–	79.00	–	–	–	–
Global Fund transaction summary[a]	15.00 (sofosbuvir) 6.40 (daclatasvir)	64.20	–	–	– 8.00 (daclatasvir)	–

Global Fund: The Global Fund to Fight AIDS, Tuberculosis and Malaria; MSF: Médecins sans Frontières; UNDP: United Nations Development Programme.
[a] Represents weighted average cost per pack.
Note: The N-dash indicates that no pricing data were available.

Innovator brand sofosbuvir is registered by Gilead Sciences as a full-strength 400 mg tablet for adults and adolescents and a half-strength 200 mg tablet for children weighing 17–35 kg. Gilead offers "access pricing" for their branded product to government programmes in 101 selected low- and middle-income countries at a flat price of US$ 250 per 28-tablet bottle, or US$ 750 for a full treatment course (*19*).

No pricing information was available for the sofosbuvir 200 mg formulation.

Availability

Sofosbuvir 200 mg and 400 mg (Sovaldi®), registered by Gilead Sciences, is approved by the FDA, European Medicines Agency, and many other regulatory authorities. Gilead Sciences has granted licences directly to a number of generic manufacturers that distribute widely. Fourteen generic suppliers have a license for drugs developed by Gilead Sciences. Eleven Indian generic suppliers are permitted to sell sofosbuvir in 105 countries.

Daclatasvir 30 mg and 60 mg (Daklinza®), registered by Bristol Myers Squibb, is approved by the US FDA, European Medicines Agency and other regulatory authorities. Daklinza® was withdrawn from the market in high-income countries in 2019 for commercial reasons and patents were allowed to expire globally. Daclatasvir licences are available through the Medicines Patent Pool in 112 countries and 10 generic suppliers currently have a sublicence for the product. More countries outside the licensed territory to the Medicines Patent Pool will soon have access to generic versions of daclatasvir as Bristol Myers Squibb announced its decision to withdraw or allow market authorization to lapse in countries where the product is no longer routinely prescribed or where other therapeutic options are available. In addition, the WHO prequalification team has designated daclatasvir a reference drug product to allow for the development of future generic products.

Many generic suppliers have sofosbuvir, daclatasvir and sofosbuvir + daclatasvir fixed-dose combination products available globally that have been prequalified by WHO or assessed by the Expert Review Panel.

Other considerations

Not applicable

Committee recommendations

The Expert Committee recommended the addition of the fixed-dose combination of daclatasvir + sofosbuvir, single-agent daclatasvir and single-agent sofosbuvir to the core list of the EMLc for the treatment of children with chronic HCV

infection among patients weighting 14 kg or more, based on evidence of pan-genotypic effectiveness and an acceptable safety profile.

The Committee noted that the results of a systematic review of trials, including trials involving daclatasvir and sofosbuvir, demonstrated high rates of virological response in children and adolescents, comparable with those observed in adults. The Committee therefore also recommended that listings of daclatasvir and sofosbuvir on the EML be extended to include adolescents. In addition, the Committee recommended the addition to the EML of the fixed-dose combination of daclatasvir + sofosbuvir and single-agent sofosbuvir 200 mg to the EML for treatment of adolescents and adults.

The Committee recognized that in paediatric patients with HCV infection and cirrhosis, co-administration of daclatasvir and sofosbuvir with ribavirin may be required. However, the Committee noted that there was limited evidence on the use of ribavirin in children and the number of children requiring ribavirin co-treatment was very small; therefore, the Committee did not recommend the inclusion of ribavirin on the EMLc.

The Committee also noted the planned inclusion of daclatasvir + sofosbuvir as one of the recommended regimens for children in the updated WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection*, the licensing agreements with the Medicines Patent Pool and the availability of prequalified and generic products.

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Sofosbuvir + velpatasvir – addition – EMLc

Sofosbuvir + velpatasvir **ATC Code: J05AP55**

Proposal

Addition of sofosbuvir + velpatasvir single-pill combination to the core list of the EMLc for the treatment of chronic hepatitis C virus infection (all genotypes) in paediatric patients.

Applicant

Clinton Health Access Initiative, Inc., United States of America

WHO technical department

Global Hepatitis Programme

EML/EMLc

EMLc

Section

6.4.4.2.1 Pan-genotypic direct-acting antiviral combinations

Dose form(s) & strength(s)

Tablet: 400 mg + 100 mg; 200 mg + 50 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The single-pill combination of sofosbuvir + velpatasvir was added to the core list of the EML in 2017 for the treatment of chronic hepatitis C virus (HCV) infection in adults based on evidence of a favourable benefit–risk ratio. Efficacy outcomes from phase II and III studies of sofosbuvir + velpatasvir showed sustained virological response rates greater than 90% in all studies and for all genotypes. Safety data indicated few discontinuations due to adverse events and a rate of serious adverse events similar to that observed with other regimens (*1*).

Public health relevance (burden of disease)

Chronic HCV infection remains a main cause of liver disease globally, with an estimated 71 million people living with chronic HCV overall as of 2015 and an estimated 1.75 million new cases a year (*2*). Previously, interferon-based therapy was long and difficult to tolerate, had a low success rate, and required extensive clinical and laboratory monitoring during treatment. The introduction of many all-oral, direct-acting antiviral treatments has led to rates of sustained virological response greater than 90% with treatment courses of 12 weeks and greatly improved safety. With these improved characteristics acknowledged, in 2016, the World Health Assembly adopted targets for the elimination of chronic HCV as a public health threat by 2030 (*3*). Treatment of chronic HCV in adults in low- and middle-income countries has been scaled up as availability of direct-acting antiviral treatments has increased.

Little emphasis has been placed on chronic HCV in children and the prevalence, epidemiology, and natural history of infection are less well understood in children than in adults. A recently-published modelling exercise estimated that 3.26 million children are living with chronic HCV infection, and 20 countries account for 80% of all cases in patients aged 0–18 years. Countries with the highest number of children with chronic HCV include China, Egypt, India, Nigeria and Pakistan (*4*). The main mode of acquisition of HCV infection in children is mother-to-child transmission, although older children and adolescents may become infected through unsafe injection practices or poor infection control practices. About 5% of infants born to mothers with HCV infection will acquire the infection, up to 10% if the mother is co-infected with HIV. The risk of transmission increases with increasing levels of maternal HCV RNA (*5*).

Most children with liver disease are asymptomatic or minimally symptomatic and cirrhosis and hepatocellular carcinoma are rare in this age group, which allows treatment to be deferred in younger children according to previous treatment guidelines. As noted in a recent publication, including children and adolescents in national HCV surveillance, testing, and treatment programmes can eventually help achieve the goal of HCV elimination (*6*).

Summary of evidence: benefits (from the application)

An innovator-sponsored trial of sofosbuvir + velpatasvir in children younger than 18 years is ongoing. To date, the trial has enrolled children with chronic HCV infection in three age groups: 12–17 years (n = 102), 6–11 years (n = 73) and 3–5 years (n = 41) from sites in Belgium, Italy, United Kingdom of Great Britain and Northern Ireland and United States of America.

In the two older age groups, about 75% of the children were infected with genotype 1 HCV, 13% had genotype 3 and smaller numbers had genotypes 2, 4 and 6. Children aged 6–11 years received 200 mg + 50 mg and those aged 12–17 years received 400 mg + 100 mg once daily for 12 weeks, after which they were monitored for 12 weeks to assess treatment response. Overall, 93.7% of the study participants achieved sustained virological response. Of the 11 children who did not achieve sustained virological response, only two experienced virological failure; in the others, the lack of sustained virological response was due to participants being lost to follow-up or spitting up or being unable to swallow the study drug. Plasma concentrations of sofosbuvir and velpatasvir in study participants were comparable to those observed in adults receiving the recommended dose (*7*).

The children aged 3–5 years received 200 mg + 50 mg once daily (weight ≥ 17 kg) or 150 mg + 37.5 mg daily, administered using an investigational granule formulation (weight < 17 kg). Mean weight in this age group was 19 kg (range 13–35 kg). It was not clear whether all children received the investigational granule formulation. The distribution of HCV genotypes in this group was: genotype 1 (78%), genotype 2 (15%), genotype 3 (5%) and genotype 4 (2%). Sustained virological response was achieved in 83% (34/41) of the children. No virological failures were documented, and the seven treatment failures were non-virological failures, either early treatment discontinuation or loss to follow-up (*8*).

An observational study evaluated sofosbuvir + velpatasvir in five children with relapsed and refractory leukaemia and active genotype 1b HCV infection undergoing allogeneic haematopoietic cell transplant. All the children achieved virological response and normalization of liver enzymes without significant adverse events during treatment. After a median of 15 months of follow-up, four of the children remained disease free and with a sustained virological response. No major drug interactions were observed with either cyclosporine or sirolimus (*9*).

Summary of evidence: harms (from the application)

To date, the number of children treated with sofosbuvir + velpatasvir is very small.

In general, sofosbuvir + velpatasvir has been shown to be well tolerated and serious adverse events are uncommon. In the ASTRAL-1 placebo-controlled registration trial in adults, the most commonly observed adverse reactions (all severity grades) in participants receiving 12 weeks of sofosbuvir + velpatasvir treatment included headache (22%), fatigue (15%), nausea (9%), asthenia (5%) and insomnia (5%). Most adverse reactions (79%) were mild and, with the exception of asthenia, occurred at a similar or lower frequency than placebo-treated patients. Participant's with cirrhosis receiving sofosbuvir + velpatasvir

plus ribavirin were more likely to have haematological abnormalities during treatment but these laboratory abnormalities occurred in less than 1% of study participants (*10*).

Sofosbuvir + velpatasvir was generally well tolerated in the paediatric trials (*7*, *8*). The most common adverse events among the 175 participants in the two older age groups included headache (23%), fatigue (18%), nausea (13%), vomiting (12%) and cough (11%). Four patients had serious adverse events reported during the trial: auditory hallucinations and constipation (two children in the younger age group), and suicidal ideation, exacerbation of bipolar disorder and suicide attempts (two adolescents in the older age group). Additional assessment of the psychiatric events showed that 27% of the study participants had some relevant psychiatric medical history (*7*). The most common adverse events observed in the 41 patients in the youngest age group were vomiting (27%), cough (15%), pyrexia (15%), rhinorrhoea (15%), fatigue (12%), nasal congestion (12%) and diarrhoea (12%). One patient in this age group discontinued treatment due to an adverse event but there were no serious adverse events. In addition, no negative effects on weight gain, height, body mass index, radiographic bone age, or sexual maturation were reported from treatment initiation to 24 weeks post-treatment in either boys or girls aged 3–17 years (*8*).

No comparative safety data with other direct-acting antiviral regimens in paediatric patients are available. A systematic review of 39 studies that evaluated the efficacy and safety of direct-acting antiviral treatments in 1796 children and adolescents reported all regimens studied, including sofosbuvir + velpatasvir, were well tolerated (*11*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

Sofosbuvir + velpatasvir is one of the three recommended pan-genotypic regimens for adults in the 2018 *WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* (*2*).

Sofosbuvir + velpatasvir is expected to be added as a treatment for adolescents and children with chronic HCV infection in the planned update to the guidelines chapter on treatment in adolescents and children. The regimen is expected be recommended as therapy for paediatric patients for whom dosing recommendations and an appropriate formulation are available. This update will be published in mid-2021 as a rapid communication policy brief, and this recommendation will also be included in the overall WHO consolidated guidelines on testing, care and treatment of viral hepatitis to be published at the end of 2021.

Costs/cost–effectiveness

Gilead Sciences offers "access pricing" for Epclusa® 400 mg + 100 mg tablets to government programmes in 101 selected low- and middle-income countries at a flat price of US$ 900 for a 12-week treatment course (*12*).

At present, there is a single generic formulation of sofosbuvir + velpatasvir 400 mg + 100 mg tablet now widely available. The United Nations Development Programme's Health Procurement Mechanism lists the price as US$ 270 for a 12-week course (*13*).

The introduction of additional generic products has the potential to substantially lower the cost of sofosbuvir + velpatasvir, as in India and Pakistan where local generic products are available. A 2020 study on the variability in cost of originator direct-acting antiviral products, reported on the availability of generic direct-acting antivirals globally and estimated the cost of production of some direct-acting antivirals (*14*).

No pricing information was available for the sofosbuvir + velpatasvir 200 mg + 50 mg formulation.

Availability

Sofosbuvir + velpatasvir 400 mg + 100 mg and 200 mg + 50 mg tablets, registered by Gilead Sciences, are approved by the US Food and Drug Administration and European Medicines Agency; voluntary licences are available in some low- and middle-income countries through the company.

To date, WHO-prequalified generic sofosbuvir + velpatasvir 400 mg + 100 mg tablets are available from Viatris (formerly Mylan Laboratories Ltd).

India and Pakistan are reported to have locally manufactured generic products.

Other considerations

The recommended dose of sofosbuvir + velpatasvir for adults and adolescents 12–17 years weighing more than 35 kg, and children 6–12 years weighing at least 30 kg (without cirrhosis) is 400 mg + 100 mg daily for 12 weeks. The approved dose for children 6–12 years weighing 17–30 kg is 200 mg + 50 mg daily for 12 weeks. Weight-based ribavirin is added to these regimens for children with cirrhosis.

Regulatory submissions to extend the weight-band dosing recommendations to children 3–5 years weighing less than 17 kg, using a dose of 150 mg + 37.5 mg daily, are currently pending.

Committee recommendations

The Expert Committee recommended the addition of the fixed-dose combination of sofosbuvir + velpatasvir to the core list of the EMLc for the

treatment of children aged 3 to 12 years with chronic HCV infection, based on evidence of pan-genotypic effectiveness and an acceptable safety profile.

The Committee noted that the results of the paediatric trial demonstrated high rates of virological response in children and adolescents, comparable with those observed in adults. The Committee therefore also recommended that listing of sofosbuvir + velpatasvir on the EML should be extended to include adolescents.

The Committee recognized that in paediatric patients with HCV infection and cirrhosis, co-administration of sofosbuvir + velpatasvir with ribavirin may be required. However, the Committee noted that there was limited evidence on the use of ribavirin in children and the number of children requiring ribavirin co-treatment was very small; therefore, the Committee did not recommend the inclusion of ribavirin on the EMLc.

The Committee also noted the planned inclusion of sofosbuvir + velpatasvir as one of the recommended regimens for children in the updated WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection*, and the availability of prequalified and generic products in some settings.

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Section 7: ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

Sumatriptan – addition – EML

Sumatriptan **ATC Code: N02CC01**

Proposal

Addition of sumatriptan to the core list of the EML for the treatment of adults with acute migraine.

Applicant

Area Farmaci e Dispositivi Medici, Direzione Generale Cura della Persona Salute e Welfare, Regione Emilia-Romagna, Italy

WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health; Bologna, Italy

WHO technical department

Department of Mental Health and Substance Use

EML/EMLc

EML

Section

7.1 Antimigraine medicines – For treatment of acute attack

Dose form(s) & strength(s)

Tablet 50 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Applications for the inclusion of sumatriptan on the EML have been considered by the Expert Committee on two previous occasions. Most recently in 2019, the Expert Committee noted that the available evidence supported the effectiveness of sumatriptan compared to placebo, but that evidence comparing sumatriptan with currently listed analgesics for migraine (acetylsalicylic acid (aspirin) and

paracetamol) showed varying results, including no difference in effect. The Committee therefore did not recommend the addition of sumatriptan to the list. However, they noted that sumatriptan is recommended as a first-line therapy for migraine in many international guidelines and requested a future review with additional data on sumatriptan in the context of other migraine therapies (*1*).

Public health relevance (burden of disease)

According to the 2019 Global Burden of Disease estimates, migraine has a global age-standardized prevalence of 14.1% (95% uncertainty interval (UI) 12.3 to 16.2) overall; 17.9% (95% UI 15.6 to 20.5) for women and 10.3% (95% UI 8.9 to 12.0) for men. About 1.13 billion (95% UI 0.98 to 1.30) people were estimated to have experienced a migraine, causing 42.1 million (95% UI 6.42 to 95.6) years of life lived with disability, corresponding to 4.8% (95% UI 0.8 to 10.1) of the total years of life lived with disability in 2019 (*2*).

Migraine has psychological, social and economic repercussions and can be associated with considerable morbidity as a result of the disability caused by frequent attacks and their treatment. Headache disorders are a public health concern given the associated disability and financial costs to society. For example, in the United Kingdom, 25 million working- or school-days are lost every year because of migraine alone (*3*), and it is estimated that more than 100 000 people are absent from work or school as a result of migraine every working day (*4*).

Summary of evidence: benefits (from the application)

The application presented evidence on the efficacy and safety of sumatriptan for treatment of acute migraine attacks in adults from two systematic reviews (*5*, *6*).

Pooled data from 18 studies showed that oral sumatriptan 50 mg was more effective than placebo for the outcome of pain freedom at 2 hours for any pain-intensity at baseline. Slightly higher estimates were observed in pooled data from 21 studies of oral sumatriptan 100 mg. The number needed to treat was considered clinically meaningful for both sumatriptan 50 mg and 100 mg for this outcome and ranged from 3 to 7. For the outcomes of headache relief at 2 hours, sustained pain freedom at 24 hours and use of rescue medication, pooled analysis also showed clinically meaningful differences and numbers needed to treat favouring sumatriptan. The certainty in the estimates was rated high, according to the GRADE framework (*5*).

Pooled data from four studies comparing sumatriptan 50 mg or 100 mg with acetylsalicylic acid 1000 mg and acetylsalicylic acid 900 mg + metoclopramide 10 mg showed a statistically significant difference in favour of sumatriptan 100 mg compared with acetylsalicylic acid 900 mg + metoclopramide 10 mg for the outcome of pain freedom at 2 hours (odds ratio (OR) 1.62, 95% confidence interval (CI) 1.17 to 2.25). In absolute terms, 26% of patients treated with sumatriptan 100 mg and 16% of those treated with

acetylsalicylic acid 900 mg + metoclopramide 10 mg were pain-free at 2 hours. The absolute risk difference was 10% in favour of sumatriptan. The difference between sumatriptan 50 mg and acetylsalicylic acid 1000 mg for pain freedom at 2 hours was not statistically significant; however the point estimate favoured sumatriptan (OR 1.22, 95% CI 0.97 to 1.53). In absolute terms, 32.2% of patients treated with sumatriptan 50 mg and 26.4% of patients treated with acetylsalicylic acid 1000 mg were pain-free at 2 hours. The absolute risk difference was 15% in favour of sumatriptan (*5*).

For the outcome of headache relief at 2 hours, sumatriptan was more effective than both acetylsalicylic acid 1000 mg, and acetylsalicylic acid 900 mg + metoclopramide 10 mg (OR 1.27, 95% CI 1.09 to 1.47). Sumatriptan 100 mg did not show a statistically significant difference compared with paracetamol 1000 mg + metoclopramide 10 mg; however, the point estimate favoured sumatriptan with an absolute risk difference of 2% in its favour. For the outcome of reduction of rescue medication use, sumatriptan was more effective than paracetamol 1000 mg + metoclopramide 10 mg (OR 0.86, 95% CI 0.74 to 0.99). For the outcome of headache relief at 1 hour, acetylsalicylic acid 1000 mg was more effective than sumatriptan 50 mg (OR 0.78, 95% CI 0.61 to 0.98) (*5*).

In comparison with other triptans, for the outcome of pain freedom at 2 hours, the efficacy of sumatriptan was comparable to other triptans, with the exception of eletriptan 40 mg and 80 mg, which showed significantly better efficacy than sumatriptan 50 mg and 100 mg. Eletriptan was also superior to sumatriptan for outcomes of headache relief at 2 and 24 hours, less use of rescue medications, and relief of migraine-associated symptoms. The certainty in the estimates was rated as high, according to the GRADE framework (*5*).

A network meta-analysis compared the relative efficacy, effectiveness and safety of triptans (alone or in combination with other drugs and for all administration routes and any dose) for treatment of acute migraine attacks in adults (> 18 years of age) compared with other triptans, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, paracetamol, ergots and opioids (*6*). To account for modification of the effect related to dosage, sumatriptan doses were categorized as low (25 mg, four randomized trials including 850 patients), standard (50 mg, 23 randomized trials including 5870 patients) and high (100 mg, 23 randomized trials including 5210 patients). Efficacy was assessed for each dosage. The systematic review provided comparative effectiveness data both from direct and indirect comparisons through a network meta-analysis. Overall, considering all administration routes, freedom from pain at 2 hours was achieved in 18% to 50% of patients with acute migraine taking standard-dose triptans. Sumatriptan provided pain freedom at 2 hours in 27.7% (95% credible interval (CrI) 24.6% to 31.0%) of patients compared with 10.6% (95% CrI 10.0% to 11.3%) of patients taking the placebo. Triptans were effective in the largest proportion of patients on the outcome headache relief at 2 hours: 41.8% (95%

CrI 32.6% to 51.5%)–75.7% (95% CrI 67.6% to 82.5%) of patients compared with 26.7% (95% CrI 25.7% to 27.7%) of patients taking the placebo. About half the patients taking sumatriptan 50 mg (49.7%, 95% CrI 46.3% to 53.1%) had headache relief at 2 hours compared with 26.7% (95% CrI 25.7% to 27.7%) of patients taking placebo.

Estimates from pairwise comparisons of sumatriptan 50 mg versus placebo showed that sumatriptan was superior to placebo for pain freedom at 2 hours and other outcomes (headache relief at 2 and at 24 hours, sustained freedom from pain at 24 hours and reduced use of rescue medication). Estimates from pairwise comparisons of sumatriptan 50 mg versus other triptans showed eletriptan 40 mg to be superior for the outcome pain freedom at 2 hours (OR 0.59, 95% CI 0.45 to 0.78) and for all the other outcomes mentioned above. These results were consistent with those observed on direct comparisons in systematic review discussed earlier (*5*).

The efficacy outcomes reported in these two systematic reviews are those recommended in the guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults (*7*).

An additional randomized controlled trial was identified that compared intranasal sumatriptan and oral sumatriptan in adults with migraine (*8*). The primary outcome was the sum of pain intensity differences 30 minutes after administration, which is not a recommended outcome measure in the guidelines of the International Headache Society. Pain freedom at 2 hours was a secondary outcome, but no statistically significant difference was found between treatment groups.

The application also presented evidence from one systematic review on the efficacy and safety of pharmacological interventions (not limited to triptans) by any route of administration for treatment of acute migraine attacks in children and adolescents (*9*). However, listing for sumatriptan was not proposed for children and adolescents because oral sumatriptan had not been studied in this population.

Summary of evidence: harms (from the application)

Among 20 049 patients treated with oral sumatriptan, only two treatment-related serious adverse events were reported: heart palpitations after treatment with sumatriptan 85 mg, and chest tightness/pressure after treatment with sumatriptan 300 mg. Withdrawals due to adverse events were uncommon: in placebo-controlled studies, excluding those using high doses of sumatriptan (> 100 mg), the proportion of patients withdrawing due to adverse events among patients treated with sumatriptan was equivalent to that of placebo (0.71% (45/6349) and 0.65% (19/2926), respectively) (*5*).

Pooled estimates of comparisons of sumatriptan versus other triptans did not show significant differences in adverse events. Acetylsalicylic acid

900 mg + metoclopramide 10 mg and paracetamol 1000 mg + metoclopramide 10 mg showed a significantly lower of adverse events than sumatriptan 100 mg (*5*). Although in migraine trials acetylsalicylic acid and paracetamol showed a lower frequency of adverse events than sumatriptan in the short term, the application noted that their long-term use at analgesic doses in patients with frequent migraine attacks posed a risk of severe and potentially life-threatening adverse events.

An industry-funded systematic review and network meta-analysis assessed the tolerability of orally administered treatments in adults with acute migraine (*10*). The review included 141 randomized controlled trials evaluating triptans, non-steroidal anti-inflammatory drugs or barbiturates in any combination, without any other limitation on sample size or treatment concealing. The quality of the included studies was not formally assessed, and the results should be interpreted with caution. Data from direct comparisons were available for sumatriptan versus placebo from 39 studies. Compared to placebo, sumatriptan was associated with a significantly higher incidence of any adverse events (OR 1.80, 95% CI 1.57 to 2.05), and treatment-related adverse events (OR 2.23, 95% CI 1.86 to 2.70). Serious adverse events were uncommon resulting in estimates with wide confidence intervals.

Data from observational studies indicate that migraine, especially migraine with aura, shows an association with ischaemic heart disease, vascular events and stroke. However, a causal relationship with migraine is unclear and the occurrence of a cerebrovascular event during a migraine attack is very rare (*11–13*). There was initial concern about the potential adverse events of sumatriptan on the cardiovascular system, especially when different centres for monitoring adverse reactions started receiving reports of chest and angina pain soon after the marketing of sumatriptan in 1992 (*14*, *15*), and postmarketing surveys of Dutch general practitioners (*16*, *17*). A meta-analysis of four observational studies assessed the risk of severe cardiovascular events associated with either recent use of or intensity of exposure to triptans or ergotamine in people with migraine (*18*). Pooled analysis showed no significant differences in the overall risk of cardiovascular events of patients with migraine treated with triptans compared with controls in relation to intensity of treatment (OR 0.86, 95% CI 0.52to 1.43). Because of the heterogeneity of the results of the included studies, pooled analysis of the risk of cardiovascular events and stroke in relation to recent use was not done.

A meta-analysis of six controlled, observational studies assessed the risk of adverse pregnancy outcomes (major congenital malformations, prematurity and spontaneous abortion) of women with migraine exposed to triptans during pregnancy compared with women with migraine not exposed to triptans and healthy women (*19*). Pooled analysis showed that the risk of major congenital malformations and prematurity was not increased in women with migraine

taking triptans during pregnancy compared with women with migraine not taking triptans. Women exposed to triptans during pregnancy had a higher rate of spontaneous abortion compared with healthy controls, although this difference was observed in only a relatively small sample of women exposed to triptans (n = 178). Women with migraine not taking triptans had a higher risk of major congenital malformations compared with healthy controls.

A systematic review by the United Kingdom's National Clinical Guideline Centre found conflicting evidence (very low quality) for adverse pregnancy outcomes from a pooled analysis of three observational studies comparing women with migraine exposed and not exposed to triptans during pregnancy (*4*). The guideline panel concluded that the evidence reviewed, although inconclusive, did not indicate an increased risk of adverse pregnancy outcomes from the use of triptans during pregnancy.

No safety data are available on the use of oral sumatriptan in children. The overall frequency of any adverse event in adolescents taking triptans is higher than placebo, although most adverse events were mild (*9*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

In 2007, WHO, in collaboration with Lifting the Burden and the European Headache Federation, published guidance on the management of common headache disorders in primary care, with a multilanguage information leaflet for patients (*20*). The guidance was based on a review of all published treatment guidelines in use in Europe and selection of the main recommendations. The guidance recommended a two-step management of acute migraine attacks, treating three attacks at each step before proceeding to the next, starting with common analgesics (such as acetylsalicylic acid, ibuprofen, diclofenac, ketoprofen, naproxen or, where these are contraindicated, paracetamol) followed, if needed, by antiemetics (such as domperidone or metoclopramide). Triptans are recommended as a second step, among specific antimigraine drugs, to be offered to all patients in whom treatment has failed in step one. The recommended starting formulation was oral; sumatriptan by subcutaneous injection was suggested when all other triptans were ineffective. Analgesics only were recommended for children.

The application identified three clinical practice guidelines that include recommendations on use of triptans for the treatment of acute migraine in adults. Sumatriptan (50 mg or 100 mg) is recommended as the first-line monotherapy treatment in adults by the Scottish Intercollegiate Guidelines Network (SIGN), with the suggestion of trying alternative triptans in case of failure (*21*). The National Institute for Health and Care Excellence (NICE)

guideline recommends an oral triptan alone or combined with a non-steroidal anti-inflammatory drug or paracetamol in adults and children. In young people (12–17 years), nasal triptan is preferred (*4*). The Canadian Headache Society guideline recommends sumatriptan, or another triptan, for moderate to severe migraine attacks in adults. If triptan alone is insufficient, its use in combination with naproxen sodium 500 mg is recommended (*22*).

In summary, there is overall consensus among the retrieved guidelines in recommending triptans (specifically, sumatriptan) as first-line treatment, or as an alternative to other analgesics in treating acute migraine attacks.

According to the SIGN and NICE guidelines, triptans can be used for treatment of acute migraine during pregnancy and in women in child-bearing age (*4*,*21*). The NICE guideline recommends balancing the potential side-effects of non-steroidal drugs, especially gastric ulceration and bleeding and cardiovascular risks, against the more rapid and prolonged benefit when used in combination with a triptan for treating an acute migraine episode (*4*).

Costs/cost–effectiveness

All triptans are currently available as unbranded generic drugs, and the cost of oral sumatriptan varies in different countries. Of all available triptans, sumatriptan is consistently the cheapest, including in low- and middle-income countries, but it is more expensive than paracetamol and acetylsalicylic acid.

The cost–effectiveness of sumatriptan in acute migraine is largely dependent on the cost of the medicine. Achieving a reduction of its average price could have a considerable impact on its cost–effectiveness when compared with less expensive alternatives, such as acetylsalicylic acid and paracetamol. If comparative cost–effectiveness modelling takes into account long-term safety, sumatriptan may become an attractive option even at its current price in situations of low willingness-to-pay by decision-makers.

Availability

Sumatriptan is available globally in branded and generic forms.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that migraine is a common disabling primary headache disorder characterized by recurrent moderate to severe pain. It is a cause of disability and results in a substantial socioeconomic burden, which is greater for women than for men.

The Committee noted that the available evidence supported the superior efficacy of sumatriptan compared with placebo. Evidence comparing

sumatriptan with currently listed analgesics (acetylsalicylic acid, paracetamol and ibuprofen) showed mixed results, which might correlate to little or no difference between currently listed analgesics and sumatriptan. The Committee also considered that the clinical use of sumatriptan is well established and it is recommended as a first-line therapy for migraine in some national and international guidelines.

The Committee considered that it was important for people with migraine to have a range of treatment options available to them, particularly for those who are at risk of specific adverse events from currently listed analgesics, those at risk of addiction and those who have little or no response to analgesics. The Committee noted that long-term use of acetylsalicylic acid, ibuprofen and paracetamol at analgesic or higher doses in patients with frequent migraine attacks poses a risk of severe adverse events (e.g. bleeding, hepatic impairment and medication-overuse headache). Sumatriptan appears to provide clinically relevant headache relief with few risks. Evidence of the safety of sumatriptan in pregnant women is still limited but, so far, accumulated data have not signalled that sumatriptan poses additional risks of birth defects compared with that in the general population.

Based on a positive benefit-to-risk profile, the Committee recommended the addition of sumatriptan to the core list of the EML for the treatment of adult patients with acute migraine. Inclusion of other triptans were not part of the application. Although the Committee thought there were likely to be benefits across the pharmacological class, few data were available on efficacy, safety, price and availability of other triptans. Therefore, the Committee did not list alternative triptans at this time, but would consider requests for listing in future.

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Section 8: IMMUNOMODULATORS AND ANTINEOPLASTICS

8.1 Immunomodulators for non-malignant disease

Tacrolimus – addition – EML and EMLc

Tacrolimus **ATC Code: L04AD02**

Proposal

Addition of tacrolimus to the EML and EMLc for prevention and treatment of graft rejection following organ transplantation.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

8.1 Immunomodulators for non-malignant disease

Dose form(s) & strength(s)

Capsules (immediate release): 0.5 mg, 0.75 mg, 1 mg, 2 mg, 5 mg
Granules for oral suspension: 0.2 mg, 1 mg
Injection: 5 mg/mL in 1 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The calcineurin inhibitor tacrolimus has not been previously considered for individual listing on the Model Lists. However, in 1999 a square box symbol

was added to the EML-listing of the calcineurin inhibitor ciclosporin for organ transplant rejection which indicated that tacrolimus could serve as an alternative to ciclosporin (*1*). Following a review of square box listings on the Model Lists in 2003, this square box was removed from the listing for ciclosporin (*2*).

Ciclosporin was added to the EML in 1991 for use following organ transplantation. The Expert Committee recognized that immunosuppressant drugs were essential for use in organ transplant programmes, where such programmes exist (*3*). Ciclosporin was included on the first EMLc in 2007 (*4*).

Public health relevance (burden of disease)

Optimal maintenance immunosuppression after organ transplant is important so that transplanted organs and transplant recipients can survive for the longest time possible. This is particularly important given the shortage of donor organs (*5*). According to Eurotransplant statistics, in 2019, 668 hearts, 1375 lungs, 1571 livers, 176 pancreases and 3191 kidneys were transplanted in Eurotransplant member countries (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands and Slovenia), with tens of thousands of people on an active waiting list (*6*).

Transplantation is the best therapy for end-stage renal failure as it improves the patient's length and quality of life, encourages occupational rehabilitation and is more cost-effective than the alternative of dialysis (*5*, *7*).

Chronic liver failure is the most common indication for liver transplantation (*8*). Other important indications are acute liver failure and hepatocellular carcinoma (*8*). The median survival after liver transplantation is more than 10 years (*9*, *10*), and there may also be an improvement in the quality of life of people with chronic liver disease after liver transplantation (*11*).

Lung transplantation has become a treatment for many people with end-stage lung diseases. Currently, more than 2700 lung transplantations are reported annually worldwide, with a 1-year survival of over 80%, and 5-year survival of 60% (*12*). Achieving long-term survival after lung transplantation is still challenging because of the occurrence of bronchiolitis obliterans syndrome and late graft failure, which are responsible for more than 40% of deaths after the first year of transplantation (*12*).

The therapeutic success of heart transplantation has been largely attributable to the development of effective and balanced immunosuppressive treatment regimens (*13*, *14*).

Summary of evidence: benefits (from the application)

Kidney transplantation

A systematic review and meta-analysis of 21 studies compared immunosuppression with tacrolimus and ciclosporin in adults (*15*). Tacrolimus

was significantly superior to ciclosporin for graft loss (relative risk (RR) 0.09, 95% confidence interval (CI) 0.06 to 0.12), acute rejection (RR 0.64, 95% CI 0.57 to 0.71) and hypercholesterolaemia (RR 0.63, 95% CI 0.54 to 0.75). No significant differences were observed between treatment groups for mortality (RR 1.07, 95% CI 0.79 to 1.45), hypertension (RR 0.96, 95% CI 0.85 to 1.08) or the frequency and type of infections (RR 1.05, 95% CI 0.92 to 1.94). An increased but non-significant risk of diabetes was seen in the tacrolimus group compared with the ciclosporin group (RR 1.89, 95% CI 1.52 to 2.35).

A systematic review and meta-analysis of 10 studies (2357 patients) compared immunosuppression with tacrolimus combined with sirolimus and tacrolimus combined with mycophenolate mofetil in adults (*16*). The authors concluded that the two treatment combinations were equally safe and effective. No significant differences were seen between treatment groups in the rates of delayed graft function, acute rejection, graft survival, infectious complications, anaemia or seroma. The tacrolimus + sirolimus group was associated with higher rates of diabetes, hyperlipidaemia and lymphocele compared to the tacrolimus + mycophenolate mofetil group.

A systematic review of 21 studies made an indirect comparison of the clinical effectiveness of tacrolimus and belatacept in adults (*17*). The authors concluded that both immediate- and prolonged-release tacrolimus were significantly superior to belatacept for acute rejection (RR 0.22, 95% CI 0.13 to 0.39 and RR 0.44, 95% CI 0.20 to 0.99, respectively). The two treatments were comparable for graft and patient survival.

A systematic review and network meta-analysis of 28 studies compared immunosuppressive efficacy of belatacept, ciclosporin and tacrolimus (*18*). Belatacept was associated with significant improvement in glomerular filtration rate compared with ciclosporin. Compared with tacrolimus, this difference was clinically meaningful but not statistically significant. The probability of being the best treatment was highest for belatacept for graft survival (68%), patient survival (97%) and renal function (89%). Tacrolimus was the immunosuppressive agent with the highest probability of being best for avoiding episodes of acute rejection (99%). Donor, recipient and trial characteristics varied across the included trials; however, little statistical heterogeneity was detected in the analysis of acute rejection, graft or patient survival, and none of the characteristics was significantly associated with the relative effect. Glomerular filtration rate in patients treated with tacrolimus was also significantly higher than in patients treated with ciclosporin (6.03 mL/min per 1.73 m^2; 95% credible interval (CrI): 1.60 to 11.00). Belatacept had significantly higher odds of acute rejection than tacrolimus (OR 2.50, 95% CrI 1.21 to 4.81). Tacrolimus had the highest probability of being best for avoiding episodes of acute rejection (*18*).

A systematic review of five studies compared immunosuppression with tacrolimus and ciclosporin in children (*19*). No significant differences were seen

between treatment groups for mortality rate (RR 1.06, 95% CI 0.59 to 1.90), graft loss (RR 0.67, 95% CI 0.40 to 1.11) or acute rejection (RR 0.79, 95% CI 0.59 to 1.05). The authors concluded that tacrolimus was as effective as ciclosporin for the outcomes of graft loss and acute rejection. However, this systematic review was considered to be of poor methodological quality by the applicants.

A systematic review of eight studies (1189 participants, age not reported) compared immunosuppression with tacrolimus and sirolimus (*20*). Pooled results did not show statistically significant differences between treatment groups for mortality (RR 0.94, 95% CI 0.46 to 1.91) or graft loss (RR 1.23, 95% CI 0.76 to 1.97). Significantly more patients treated with sirolimus experienced acute rejection (RR 2.08, 95% CI 1.47 to 2.95). The risk of infection was significantly lower with sirolimus (RR 0.43, 95% CI 0.26 to 0.72). Patients treated with sirolimus were significantly more likely to be withdrawn from treatment because of adverse events (RR 1.93, 95% CI 1.32 to 2.83) than patients treated with tacrolimus.

A Cochrane systematic review of 30 studies (4102 participants) compared immunosuppression with tacrolimus and ciclosporin in adults and children (*21*). At 6 months, the risk of graft loss was significantly lower in patients treated with tacrolimus (RR 0.56, 95% CI 0.36 to 0.86) and this effect persisted up to 3 years. At 1 year, tacrolimus patients had a lower risk of acute rejection (RR 0.69, 95% CI 0.60 to 0.79) and steroid-resistant rejection (RR 0.49, 95% CI 0.37 to 0.64), but more diabetes mellitus requiring insulin (RR 1.86, 95% CI 1.11 to 3.09), and tremor (RR 2.18, 95% CI 1.50 to 3.17), headache (RR 1.23, 95% CI 1.00 to 1.52), diarrhoea (RR 1.98, 95% CI 1.03 to 3.83), dyspepsia (RR 1.31, 95% CI 1.00 to 1.70) and vomiting (RR1.41, 95% CI 1.05 to 1.89). Patients treated with ciclosporin experienced significantly more constipation and cosmetic side-effects. There was no difference in infection or malignancy between patients treated with tacrolimus or ciclosporin. Compared with ciclosporin, recipients of kidney transplants treated with tacrolimus showed substantial improvement in graft survival, with a 44% reduction in graft loss (censored for death) within the first 6 months of transplantation. Treatment with tacrolimus led to 31% fewer patients experiencing acute rejection and 51% fewer experiencing severe rejection episodes that required more intensive therapy than steroids, within the first year of transplantation.

Liver transplantation

A Cochrane systematic review of 23 trials (3693 participants) evaluated the benefits and harms of maintenance immunosuppression interventions in adults with liver transplants (*22*). The pair-wise meta-analysis of ciclosporin and tacrolimus showed that ciclosporin was associated with more retransplantation than tacrolimus (very low quality evidence, hazard ratio (HR) 3.08, 95% CrI 1.13 to 9.90). Low-quality evidence from direct comparison of ciclosporin

and tacrolimus showed similar results (HR 3.07, 95% CrI 1.12 to 8.38). The combination of tacrolimus and sirolimus showed higher mortality and graft loss (HR 2.76, 95% CrI 1.30 to 6.69 and HR 2.34, 95% CrI 1.28 to 4.61, respectively) compared with tacrolimus alone. However, this finding was from a direct comparison in a single trial including 222 participants (low-certainty evidence). No differences were found between the two treatments based on network meta-analysis results (very low-certainty evidence).

A systematic review of 11 trials compared tacrolimus versus ciclosporin as primary immunosuppression in adults with liver transplants (*23*). Mortality in patients given ciclosporin was significantly higher than in patients treated with tacrolimus (RR 1.26, 95% CI 1.01 to 1.58) as was the risk of hypertension (RR 1.26, 95% CI 1.07, 1.47). Ciclosporin was associated with a lower risk than tacrolimus of developing new-onset diabetes after transplantation (RR 0.60, 95% CI 0.47 to 0.77). No significant differences were found for graft loss or acute rejection.

These findings are consistent with the findings of an earlier systematic review and meta-analysis of 16 randomized trials comparing tacrolimus and ciclosporin (3813 participants) (*24*). Most of the trials restricted enrolment to adults, but one included children and one was restricted to children. At 1 year, mortality (RR 0.85, 95% CI 0.73 to 0.99) and graft loss (RR 0.73, 95% CI 0.61 to 0.86) were significantly lower in patients treated with tacrolimus. Patients treated with tacrolimus also had a lower risk of acute rejection (RR 0.81, 95% CI 0.75 to 0.88) and steroid-resistant rejection (RR 0.54, 95% CI 0.47 to 0.74) in the first year. No differences were seen with lymphoproliferative disorder or new dialysis rates, but more new insulin-requiring diabetes mellitus occurred in the tacrolimus group (RR 1.38, 95% CI 1.01 to 1.86). The risk of withdrawal from the drug was lower for tacrolimus than ciclosporin (RR 0.57, 95% CI 0.49 to 0.66).

A systematic review and meta-analysis of 14 studies (1814 participants) evaluated the efficacy of immunosuppression monotherapy in adults (*25*). Tacrolimus and ciclosporin monotherapy were found to be as effective as immunosuppression with steroid-based combination therapy and associated with fewer complications. Tacrolimus monotherapy did not increase hepatitis C virus infection recurrence in hepatitis C virus-infected liver transplant recipients.

Lung transplantation

A Cochrane systematic review of three studies (413 participants) compared tacrolimus with ciclosporin for primary immunosuppression in adult patients with lung transplant (*26*). No significant differences were seen between treatment groups for mortality (RR 1.06, 95% CI 0.75 to 1.49), incidence of acute rejection (RR 0.89, 95% CI 0.77 to 1.03), number of infections/100 patient-days (mean difference (MD) –0.15, 95% CI –0.30 to 0.00), cancer (RR 0.21, 95% CI 0.04 to 1.16), kidney dysfunction (RR 1.41, 95% CI 0.93 to 2.14), kidney failure (RR

1.57, 95% CI 0.28 to 8.94), neurotoxicity (RR 7.06, 95% CI 0.37 to 135.19) and hyperlipidaemia (RR 0.60, 95% CI 0.30 to 1.20). Tacrolimus was significantly superior to ciclosporin regarding the incidence of bronchiolitis obliterans syndrome (RR 0.46, 95% CI 0.29 to 0.74), lymphocytic bronchitis score (MD −0.60, 95% CI −1.04 to −0.16), treatment withdrawal (RR 0.27, 95% CI 0.16 to 0.46) and arterial hypertension (RR 0.67, 95% CI 0.50 to 0.89). No significant difference was seen for arterial hypertension when analysed using a random-effects model (RR 0.54, 95% CI 0.17 to 1.73). Diabetes mellitus occurred more frequently in patients receiving tacrolimus than those receiving ciclosporin when the fixed-effect model was applied (RR 4.24, 95% CI 1.58 to 11.40), but no statistically significant difference was found using the random-effects model (RR 4.43, 95% CI 0.75 to 26.05). The included studies were considered to have a high risk of bias.

A systematic review of three studies (297 participants) evaluated the benefits and harms of tacrolimus versus ciclosporin as primary immunosuppression in adults (*27*). No significant difference was found in 1-year mortality between treatment groups (odds ratio (OR) 0.94; 95% CI 0.42 to 2.10). Patients treated with tacrolimus had fewer incidences of acute rejection (MD −0.14, 95% CI −0.28 to −0.01). Pooled analysis showed a lower risk of bronchiolitis obliterans syndrome in the tacrolimus group, although this was not statistically significant (OR 0.53, 95% CI 0.25 to 1.12). Fewer treatment withdrawals were seen in the tacrolimus group (OR 0.12, 95% CI 0.03 to 0.48). The likelihood of new-onset diabetes was higher in the tacrolimus group (OR 3.69, 95% CI 1.17 to 11.62). The incidence of hypertension and renal dysfunction were comparable between tacrolimus and ciclosporin (OR 0.24, 95% CI 0.03 to 1.70 and OR 1.67, 95% CI 0.70 to 3.96, respectively). The point estimate suggested a lower risk of malignancy in patients treated with tacrolimus, although this was not statistically significant (OR 0.19, 95% CI 0.03 to 1.13). The incidence of infection was comparable between the two treatments (MD −0.29, 95% CI −0.68 to 0.11).

Heart transplantation

A systematic review and meta-analysis of 11 studies (952 participants) evaluated primary immunosuppression with tacrolimus versus ciclosporin in adults and paediatric patients with heart transplant (*28*). No significant differences were found between the treatments for mortality (RR 0.78, 95% CI 0.54 to 1.13), grade 3A or higher rejection (RR 0.86, 95% CI 0.62 to 1.20), infection (RR 1.01, 95% CI 0.84 to 1.21) or basal cell skin cancer (comparison with microemulsion ciclosporin) (RR 1.20, 95% CI 0.29 to 4.93). Patients treated with tacrolimus had significantly lower risk of hypertension (RR 0.80, 95% CI 0.69 to 0.93), hyperlipidaemia (RR 0.57, 95% CI 0.44 to 0.74) and hirsutism (comparison with microemulsion ciclosporin; RR 0.17, 95% CI 0.04 to 0.62). The risk of diabetes

was higher in patients treated with tacrolimus but this was not statistically significant (RR 1.35, 95% CI 0.93 to 1.94). In addition, no significant differences were seen between treatment arms for renal failure requiring haemodialysis, chronic allograft vasculopathy or neurotoxicity.

A systematic review and meta-analysis of seven studies (885 participants) compared the benefits and harms of tacrolimus and microemulsion ciclosporin for primary immunosuppression in adults and children (*29*). No statistically significant difference was found in mortality at 1 year between treatment groups (RR 0.70, 95% CI 0.45 to 1.08). Tacrolimus was associated with significantly lower risks of acute rejection at both 6 months and 1 year (RR 0.61; 95% CI 0.49 to 0.75 and RR 0.69, 95% CI 0.48 to 0.98, respectively). Fewer patients taking tacrolimus than microemulsion ciclosporin stopped treatment (RR 0.57, 95% CI 0.40 to 0.83) and experienced post-transplant hypertension (RR 0.88, 95% CI 0.81 to 0.96). The rate of new-onset diabetes mellitus requiring insulin treatment was higher with tacrolimus using a fixed-effects model (RR 1.65, 95% CI 1.18 to 2.29), however no difference was found using a random-effects model. The incidence of malignancy and renal failure requiring dialysis were comparable between treatment groups.

Summary of evidence: harms (from the application)

The most frequently reported adverse effects of tacrolimus include new-onset diabetes mellitus following transplantation, neurological effects, gastrointestinal complications (nausea, vomiting, diarrhoea and dyspepsia), changes in renal function, cardiotoxicity, tremor, headache and hyperkalaemia.

A systematic review of 54 studies evaluated the reported incidence of new-onset diabetes mellitus in adult solid-organ transplant recipients receiving treatment with calcineurin inhibitors (tacrolimus and ciclosporin) (*30*). Overall, new-onset diabetes mellitus was reported in 13.4% of transplant recipients, with a higher incidence occurring in patients receiving tacrolimus than ciclosporin (16.6% versus 9.8%). The trend was observed across all transplant groups studied. The results of a meta-analysis of 16 studies found the frequency of insulin-dependent diabetes mellitus to be significantly higher in patients treated with tacrolimus (10.4% versus 4.5%; $P < 0.001$).

A systematic review of 10 studies (2357 participants) found that sirolimus combined with tacrolimus may lead to higher rates of diabetes, hyperlipidaemia and lymphocele compared with a combination of tacrolimus and mycophenolate mofetil (*16*). This is in line with the results of a three-arm, multicentre randomized controlled trial that showed a trend toward less diabetes in the steroid-free group containing daclizumab induction, tacrolimus and mycophenolate mofetil (*31*). When treatment based on ciclosporin plus azathioprine was compared with tacrolimus plus mycophenolate mofetil, no significant difference was seen in

the incidence of diabetes after transplantation (*32*). Tacrolimus in combination with 2 g/day mycophenolate mofetil showed the lowest incidence of new diabetes mellitus compared with tacrolimus and azathioprine or 1 mg/day mycophenolate mofetil (*33*). Similar results were found in a randomized trial of 538 adult renal transplant patients which reported a significantly lower incidence of insulin-dependent diabetes if treatment was based on the combination of daclizumab, tacrolimus and mycophenolate mofetil (5.4% versus 0.4%; $P = 0.003$) (*34*).

Gastrointestinal complications were more likely in patients treated with tacrolimus than those treated with ciclosporin; however, patients given tacrolimus were less likely to experience viral infections and hypertension (*35*).

No differences have been seen between tacrolimus and ciclosporin for kidney dysfunction (RR 1.41, 95% CI 0.93 to 2.14), kidney failure (RR 1.57, 95% CI 0.28 to 8.94) or kidney failure requiring haemodialysis (RR 1.45; 95% CI 0.50–4.26) (*26*, *28*) . However, a study that monitored mean creatinine levels at 5 years showed preserved renal function in patients given sirolimus and mycophenolate mofetil versus the tacrolimus and mycophenolate mofetil treatment (*36*).

There is consistent evidence of no difference in neurotoxicity between tacrolimus and ciclosporin, as well as no difference in the rates of stroke (*28*). No difference was observed in the frequency and type of infections between tacrolimus and ciclosporin (*28*). When sirolimus is combined with tacrolimus, higher rates of infectious complications have been found, however they were not statistically significant (*16*).

In general, there was no difference in the malignancy rates in patients treated with tacrolimus compared with ciclosporin, with one study showing a trend toward lower risk of malignancy in patients treated with tacrolimus (*21*). The incidence of malignancies and opportunistic infections was low and similar for both tacrolimus and ciclosporin (*27*).

A systematic review of five studies (923 participants) compared the effects of tacrolimus and ciclosporin on metabolic syndrome and cardiovascular risk factors after renal transplantation in adults (*37*). Compared to ciclosporin, tacrolimus treatment was associated with a lower incidence of hyperlipidaemia (RR 0.50, 95% CI 0.39 to 0.64) and hypertension (RR 0.91, 95% CI 0.83 to 1.00); the difference for hypertension was not significant.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the prevention and management of organ transplant rejection are not currently available.

The use of tacrolimus for induction and maintenance of immunosuppression following solid organ transplant is recommended in the following national and international guidelines.

- Immunosuppressive therapy for kidney transplant in adults (*38*). Immunosuppressive therapy for kidney transplant in children and young people (*39*). National Institute for Health and Care Excellence (NICE) (2017)
- Renal Association. Clinical practice guidelines – standardisation of immunosuppressive and anti-infective drug regimens in UK paediatric renal transplantation: the harmonisation programme (2020) (*40*)
- European Association of Urology. EAU guidelines on renal transplantation (2018) (*41*)
- Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients (2010) (*42*)
- Renal Association clinical practice guideline in post-operative care in the kidney transplant recipient (2017) (*43*)
- Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care (2020) (*44*)
- Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association (2015) (*45*)
- Monitoring of nonsteroidal immunosuppressive drugs in patients with lung disease and lung transplant recipients: American College of Chest Physicians evidence-based clinical practice guidelines (2012) (*46*)
- Adult liver transplantation: UK clinical guideline – part 2: surgery and post-operation (2020) (*47*)
- European Association for the Study of the Liver. EASL clinical practice guidelines: liver transplantation (2016) (*48*)
- Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation (*49*)

Costs/cost-effectiveness

Immediate-release tacrolimus is considered a cost-effective and clinically effective option for preventing organ rejection in children, young people

and adults having a kidney transplant (*38*, *39*). Based on a health technology assessment report of 16 tacrolimus combinations, the only cost-effective combination was basiliximab induction followed by maintenance with immediate-release tacrolimus and mycophenolate mofetil at an incremental cost of £ 20 000–30 000 per quality-adjusted life year (*50*). Mycophenolate mofetil used together with tacrolimus is a cost-effective use of resources for preventing organ rejection in children and young people having a kidney transplant (*39*). Twice daily tacrolimus with mycophenolate mofetil and corticosteroids were found to be more cost-effective than belatacept in terms of acute rejection outcomes in adult kidney transplant patients (*17*).

A study comparing the costs of tacrolimus versus ciclosporin treatment (resource-use quantities, cost of drugs, concomitant medications, hospitalization, dialysis and rejection episodes) in 50 centres in western European countries found that per-patient savings with tacrolimus ranged from € 524 to € 1776. Most of the savings were due to shorter initial hospital stay, fewer rehospitalizations, lower cost of immunosuppressive drugs for graft rejection and lower incidence of dialysis (*51*).

Compared to sirolimus, tacrolimus was found to be a more-cost effective treatment for preventing adverse events after renal transplantation because it reduces the incidence of graft rejection and the cost of treatment with steroids and antibody therapy (*52*).

Prolonged-release tacrolimus administered orally as one capsule a day was not found to be cost-effective (*39*, *50*).

Availability

Immediate-release tacrolimus is available globally as originator and generic products.

Other considerations

Evidence on bioequivalence of generic and brand-name tacrolimus is limited and is not consistent across various studies.

Data from observational studies involving kidney transplant patients who were switched from immediate-release originator tacrolimus to a generic tacrolimus suggested this switch was feasible and appeared to be safe, but required careful monitoring of patient trough concentrations for tacrolimus, plasma creatinine levels and overall patient status (*53*, *54*). The change resulted in cost savings, despite the cost of extra monitoring (*54*). Similar results were found in another study of stable liver transplant patients who were switched to generic tacrolimus and followed for 6 months: the generic medicine was is effective and seemed to be safe and cost-efficient (*55*).

A systematic review, mostly based on observational data and studies with some risk of bias, concluded that there was no significant difference in

biopsy-proven acute rejection rates between generic and brand-name tacrolimus and even found some evidence suggesting a lower risk of biopsy-proven acute rejection with generic tacrolimus (*56*).

However, unlike evidence from observational studies, a randomized cross-over trial involving stable elderly kidney transplant patients found that generic and originator immediate-release tacrolimus were not bioequivalent. Patients on generic tacrolimus had significantly higher levels of systemic drug exposure, which may increase the likelihood of nephrotoxicity and other adverse effects (*57*).

Committee recommendations

The Expert Committee noted the unmet public health need for prevention and treatment of rejection in organ transplantation. Tacrolimus has been studied for over 25 years as an immunosuppressant specifically focused on reducing graft rejection after transplantation. Originally studied in liver transplant patients, a series of trials has expanded its use to a wide range of other types of organ transplants.

Tacrolimus has been in wide clinical use for many years and it is licensed for use in children and adults in several countries. The EML currently lists azathioprine and ciclosporin as immunomodulators for use in organ transplantation. The Committee acknowledged that the available evidence suggests that tacrolimus is superior to ciclosporin with regard to graft loss and acute rejection.

Based on these considerations and the overall favourable efficacy and toxicity profile of tacrolimus, the Committee recommended the inclusion of immediate-release tacrolimus on the complementary list of the EML and EMLc for use in organ transplantation.

The Committee recognized that as the indication is for organ transplantation, tacrolimus would only be used in settings where organ transplantation is available and affordable. The Committee also recognized that avoiding transplant rejection and graft loss is very important in these settings given the considerable resources invested in transplantation and the scarcity of donor organs.

The Committee also noted that given its narrow therapeutic window, therapeutic drug monitoring of tacrolimus blood levels is important in the context of transplantation and recommended by most international guidelines. The Committee therefore requested that therapeutic drug monitoring for tacrolimus should be evaluated for inclusion in the next edition of the WHO model list of essential in vitro diagnostics.

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8.2 Antineoplastics and supportive medicines

8.2.1 Cytotoxic medicines

Azacitidine – addition – EML

Azacitidine **ATC Code: L01BC07**

Proposal

Addition of azacitidine to the complementary list of the EML for the treatment of acute myeloid leukaemia in adults.

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WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that, in line with the recommendation from the EML Cancer Medicines Working Group, there is insufficient evidence to justify the inclusion of azacitidine on the EML at this time.

EML/EMLc

EML

Section

8.2.1 Cytotoxic medicines

Dose form(s) & strength(s)

Azacitidine: powder for injection 100 mg in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Azacitidine has not previously been considered for inclusion on the EML.

Cytarabine and daunorubicin were included on the EML for induction and consolidation therapy of acute myeloid leukaemia following a comprehensive review of cancer medicines undertaken by the Expert Committee in 2015 (*1*).

Public health relevance (burden of disease)

Acute myeloid leukaemia is a common leukaemia subtype and has a poor prognosis.

Globally, almost 120 000 incident cases of acute myeloid leukaemia were recorded in 2017, with an age-standardized incidence rate of 1.54 per 100 000. Geographically, the highest burden is seen in South Asia and Western Europe regions. Since 1990, the number of deaths related to acute myeloid leukaemia worldwide has almost doubled, from 52 000 to 100 000 in 2017 (*2*).

Most incident cases of acute myeloid leukaemia occur in adults older than 65 years, and this group has a particularly poor prognosis. Patients with acute myeloid leukaemia have a lower baseline quality of life than individuals with other cancers, and the quality of life may be greatly affected because of the treatment (*3*).

Summary of evidence: benefits (from the application)

The applicants conducted a literature search for randomized trials and systematic reviews of azacitidine used in treatment of acute myeloid leukaemia and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool, and judgements about precision, consistency, directness and likelihood of publication bias were made following the GRADE approach.

Four systematic reviews (*4–7*) (used to identify relevant studies) and nine randomized trials (*8–16*) were identified.

In general, trials included patients older than 65 years and randomized participants to receive azacitidine or a conventional treatment regimen (standard chemotherapy, cytarabine in low dose, lenalidomide or observation only). In most of the identified trials, azacitidine was used during the induction phase. It was used only in the consolidation phase after induction with standard chemotherapy in four trials (*9*, *13*, *14*, *16*).

The meta-analysis undertaken by applicants included six trials (1125 participants) and showed that the use of azacitidine in patients with acute myeloid leukaemia might increase overall survival by about 0.2 months (hazard ratio (HR) 0.96, 95% confidence interval (CI) 0.69 to 1.35). The certainty of the evidence was judged low due to imprecision (because the CI does not exclude potential harm with azacitidine) and inconsistency (because of unexplained heterogeneity introduced by one trial (*15*)).

Summary of evidence: harms (from the application)

Compared with standard chemotherapy, azacitidine may not increase the risk of adverse events. From the nine trials (1409 participants) included in the meta-analysis, a similar incidence of adverse events was observed with or without azacitidine (relative risk (RR) 0.99, 95% CI 0.80 to 1.23; low-certainty evidence). The most commonly reported adverse events were febrile neutropenia, thrombocytopenia, infection and gastrointestinal symptoms.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of acute myeloid leukaemia are not available.

Costs/cost–effectiveness

The applicants identified four cost–utility analyses that evaluated the cost–effectiveness of azacitidine for treatment of acute myeloid leukaemia (*17*) or myelodysplastic syndromes (*18–20*). One study was excluded from the evidence synthesis due to serious limitations making the results unreliable (*20*).

A cost-utility analysis was done from a third payer perspective based on the Canadian health system (*17*). Using a 25-month time horizon, the base-case incremental cost–effectiveness ratio for azacitidine compared with conventional care regimens was 160 438 Canadian dollars (Can$) per quality-adjusted life year (QALY) gained. The incremental cost–effectiveness ratio was similar using a life-time horizon (Can$ 160 373 per QALY). Incremental cost–effectiveness ratios in the range of Can$ 50 000–140 000 per QALY gained have been reported for Canadian reimbursement decisions.

The cost–utility analyses conducted for azacitidine in myelodysplastic syndromes reported less favourable incremental cost–effectiveness ratios. However, this indication was not considered by the application.

The applicants report that national reimbursement agencies in Australia, Peru and the United Kingdom of Great Britain and Northern Ireland have evaluated the cost–effectiveness of azacitidine and, despite ratios higher than

standard reimbursement thresholds, they recommended coverage because of the lack of other effective treatments in individuals unsuitable for intensive chemotherapy.

Availability

Azacitidine has marketing approval from many national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. It is available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group advised that it does not support the inclusion of azacitidine injection on the EML for the treatment of acute myeloid leukaemia.

The Working Group noted that the observed magnitude of benefit for azacitidine in acute myeloid leukaemia in terms of overall survival is modest, and below the threshold for benefit established for EML consideration. The Working Group recognized that acute myeloid leukaemia is a disease with a poor prognosis and an unmet clinical need for effective treatment exists, particularly for older patients (> 60 years). However, azacitidine is not a curative treatment option and provides only a small benefit.

Committee recommendations

The Expert Committee noted that despite the substantial unmet need for effective therapy for acute myeloid leukaemia in patients unsuitable for intensive induction chemotherapy, the clinical impact of injectable azacitidine on survival is small when compared with other medicines listed in the EML, such as cytarabine and daunorubicin. Moreover, treatment with azacitidine is associated with substantial toxicity and increases the need for high-level supportive care, such as red cell and platelet transfusions and antibiotic treatments. Clearer definition of subgroups of patients who benefit the most in terms of increased survival and more compelling evidence of efficacy in the maintenance setting are required before injectable azacitidine could warrant reconsideration. The Committee also noted that, despite the availability of generic formulations, prices are still high and are an important barrier to access in many countries.

Therefore, the Committee recommended that azacitidine for acute myeloid leukaemia should not be added to the complementary list of the EML at this time.

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Cancer medicines for low-grade glioma – new indication – EML and EMLc

Carboplatin	**ATC Code: L01XA02**
Cisplatin	**ATC Code: L01XA01**
Cyclophosphamide	**ATC Code: L01AA01**
Vinblastine	**ATC Code: L01CA01**
Vincristine	**ATC Code: L01CA02**

Proposal

Extension of the indications for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine on the complementary list of the EML and EMLc to include treatment of low-grade glioma in children and adolescents.

Applicant

European Society for Paediatric Oncology (SIOP Europe)

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that, in line with the recommendation from the EML Cancer Medicines Working Group, the inclusion of the indication of low-grade glioma for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine on EMLc is appropriate. These medicines and accompanying treatment protocols are well established, recognized as the standard of care and associated with clinical benefits, including improved survival and reduction in the long-term sequelae from alternate treatments. The extension of the indication for these medicines also supports the effort the WHO Global Initiative for Childhood Cancer, which has low-grade glioma as one of the six priority cancers.

EML/EMLc

EML and EMLc

Section

8.2.1 Cytotoxic medicines

Dose form(s) & strength(s)

Carboplatin: injection 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL, 600 mg/60 mL
Cisplatin: injection 10 mg/10 mL, 20 mg/20 mL, 50 mg/50 mL, 100 mg/100 mL
Cyclophosphamide: powder for injection 200 mg, 500 mg, 750 mg, 1000 mg and 2000 mg in vial
Vinblastine: injection 10 mg/10 mL
Vincristine: injection 1 mg/mL, 2 mg/2 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Chemotherapy for the treatment of low-grade glioma has not previously been considered by the Expert Committee.

All the proposed medicines are currently included on the EML and EMLc for other cancer indications.

Public health relevance (burden of disease)

Brain tumours are the largest group of solid tumours in children and account for about one quarter of all cancers in children younger than 15 years. Low-grade gliomas are the most common paediatric brain tumours, estimated to account for around 40% of all central nervous system tumours in children younger than 18 years (*1*). The annual incidence of paediatric low-grade glioma is 10 per 1 million in high-income countries. Incidence rates vary among high-, middle- and low-income countries; data are not available for some regions where imaging methods required for diagnosis or centralized cancer registries are not available (*2*). The median age at diagnosis is 6 to 8 years (*3*).

Low-grade gliomas are WHO grade I and II tumours (*4*) of glial origin; they are rather slow-growing tumours. Low-grade gliomas can occur anywhere in the brain and spinal cord, but most appear in the cerebral and cerebellar hemispheres. Dissemination develops in only a very small proportion of patients (5–10%). Low-grade gliomas can be associated with cancer predisposition syndromes, such as neurofibromatosis type 1 and tuberous sclerosis complex.

The clinical course of low-grade glioma is very varied and not always predictable at diagnosis. Age at diagnosis, histological subtype and biological tumour characteristics all affect the clinical course. Some low-grade gliomas do not need treatment but are monitored to follow the clinical course, other types need neurosurgery or chemotherapy only, and other types need a combination of chemotherapy and radiotherapy.

In general, low-grade gliomas have a 10-year overall survival rate of 90–95% and 10-year progression-free survival rate of around 44% (*3*,*5*). However, these rates might differ for some subtypes or if additional risk factors are present, such as BRAF V600E mutation. Low-grade glioma is considered a chronic disease with periods of stable disease, followed by progressive tumour growth needing treatment, followed by a stable period again. The effectiveness and feasibility of repeated chemotherapy in progressive low-grade glioma has

been shown in a small trial (38 patients) to result in 5-year overall survival and progression-free survival rates of 86% and 37%, respectively (*6*).

Summary of evidence: benefits (from the application)

The International Society of Paediatric Oncology–Low Grade Glioma trial (SIOP-LGG-2004 trial) is a cooperative multicentre randomized controlled trial for children and adolescents with low-grade glioma, without neurofibromatosis type 1-associated visual pathway glioma at high risk of progression (*7*). Paediatric oncology societies from 11 European countries participated in this trial, which consisted of two arms: (i) standard chemotherapy induction (vincristine, carboplatin), or (ii) intensified chemotherapy induction (vincristine, carboplatin, etoposide).

Both treatments were followed by a consolidation phase with vincristine and carboplatin, or, in case of allergy or early progression, with vincristine, cisplatin and cyclophosphamide.

Standard induction consisted of 10 weekly doses of vincristine 1.5 mg/m² by intravenous (IV) bolus and four doses of carboplatin 550 mg/m² by IV infusion at 3-week intervals followed by three cycles of simultaneous vincristine and carboplatin at 4-week intervals. Intensification with etoposide 100 mg/m² by IV infusion was added on days 1–3 in weeks 1, 4, 7 and 10. For consolidation, patients in both arms received 10 6-week cycles of vincristine 1.5 mg/m² IV on days 1, 8 and 15 and carboplatin 550 mg/m² IV on day 1. The total duration of chemotherapy was 18 months. Dose modifications were advised for children weighing less than 10 kg and for children younger than 6 months. Dose reductions were prescribed in case of haematological or organ toxicity. Grade I hypersensitivity reactions to carboplatin permitted the repeated administration under close surveillance, premedication and slowed infusion rate. In cases of Grade II or higher hypersensitivity reactions, replacement of carboplatin with cycles of cisplatin (30 mg/m², day 1 and 2) and cyclophosphamide (1500 mg/m², day 1) was recommended (*7*).

One of the aims of the SIOP-LGG-2004 trial was to determine if etoposide added to standard induction with vincristine and carboplatin increased progression-free survival. The trial found no difference in terms of survival and radiological response between the two arms. The 5-year progression-free survival and overall survival were 46% and 89%, respectively, in the vincristine/carboplatin arm and 45% and 89%, respectively in the vincristine/carboplatin/etoposide arm. If the same progression-free survival and overall survival can be reached with a two-drug regimen, this is preferred over a three-drug regimen, especially because etoposide is also known to cause considerable late effects, such as secondary haematological malignancies. These results support the role of vincristine and carboplatin as the standard of care for induction chemotherapy for low-grade glioma. Subgroup analyses of the SIOP-LGG-2004 trial also show

the benefit of vincristine plus carboplatin in terms of overall survival in patients with low-grade glioma of the brainstem (*8*), tectal plate (*9*) and thalamus (*10*).

Vinblastine monotherapy is used in first- and second-line treatment of low-grade glioma. A phase II study evaluated the efficacy of vinblastine 6 mg/m² administered once a week for 70 weeks in 54 paediatric patients who had not received prior chemotherapy for progressive low-grade glioma. The time to best response was 52 weeks. The total response rate was 25.9%: one complete response, nine partial responses and four minor responses. Thirty-four patients had stable disease and six patients had progressive disease. After median follow-up of 5 years, the 5-year overall survival was 94.4% and 5-year progression-free survival was 53.2%. Two thirds of participants required a reduction in vinblastine dose, mainly due to haematological toxicity (neutropenia) (*11*).

Another phase II study evaluated the efficacy of vinblastine 6 mg/m² administered once a week for 1 year in 50 paediatric patients with recurrent or refractory low-grade glioma. The median time to best response was 12 months. The total response rate was 36%: one complete response, 10 partial responses and seven minor responses. Nineteen patients had stable disease and 13 patients had progressive disease. After median follow-up of 67 months, the 5-year overall survival rate was 93.2% and the estimated 5-year event-free survival was 42.3% (*12*).

Summary of evidence: harms (from the application)

The most commonly reported grade 3 and 4 toxicities associated with the vincristine plus carboplatin regimen in the SIOP-LGG-400 trial were haematological events, infection and nausea/vomiting. Thirty-one patients experienced at least one allergic event to carboplatin (*7*).

In the phase II studies of vinblastine monotherapy, overall, treatment was well tolerated. The most frequently reported adverse events were haematological events (neutropenia), infection and fever (*11*, *12*).

Additional evidence (not in the application)

Not applicable.

WHO guidelines

WHO guidelines for the treatment of low-grade glioma are not available. However, low-grade glioma is one of the six tracer cancers in the WHO Global Initiative for Childhood Cancer. This initiative seeks to increase countries' capacity to provide quality services for children with cancer, and increase prioritization of childhood cancer at national, regional and global levels. The goal of the initiative is to achieve a 60% survival rate for children with cancer by 2030 and reduce suffering from childhood cancer globally.

Costs/cost–effectiveness

Based on vial prices from the Netherlands, a single treatment course of induction and consolidation chemotherapy with vincristine and carboplatin for a child with body surface area of 1 m^2 is estimated to cost about € 4172. A single treatment course of vinblastine monotherapy for a child with body surface area of 1 m^2 is estimated to cost about € 1983. The total duration of treatment (number of treatment courses) can vary largely between patients, due to the heterogeneous nature of the clinical course of low-grade glioma.

Availability

Carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine are already included on the EML and EMLc and are available globally in branded and generic versions.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the expansion of the listings on the EMLc for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine to include the indication of low-grade glioma.

The Working Group recognized that the evidence presented is not always from large randomized controlled trials, but that the treatment protocols are associated with relevant benefits and are recognized as the standard of care for treatment of paediatric low-grade glioma and this supports the inclusion of these medicines on the EMLc. The Working Group acknowledged that the availability of clinical evidence in paediatrics was limited but considered that obtaining the usual level of evidence required for EML listings was unlikely. In this case, efficacy and safety could be accepted based on extrapolation of the well known benefits and harms from use of these medicines in adults, for other indications in children and as part of standard cancer care in children.

Noting that the EMLc lists medicines for the treatment of children up to 12 years of age, and that low-grade glioma also affects older children and adolescents, the Working Group also supports inclusion of these medicines on the EML for this indication.

Expanding the EMLc indications for these medicines would also support the goals of WHO's Global Initiative for Childhood Cancer and contribute towards the achievement of the best possible cancer care for children.

Committee recommendations

The Expert Committee noted that low-grade glioma is the most common type of paediatric brain tumour and is one of the priority paediatric cancers in WHO Global Initiative for Childhood Cancer.

Despite the limitation in the evidence presented in the application, treatment protocols including carboplatin, cisplatin, cyclophosphamide,

vinblastine and vincristine in low-grade glioma are recognized as the standard of care and are associated with some benefits. Therefore, the Committee recommended the extension of current listings on the complementary list of the EML and EMLc for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine to include the indication low-grade gliomas. The Committee also recommended the inclusion of additional formulations and strengths of cisplatin, vinblastine and vincristine as proposed in the application.

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Cancer medicines for children – new indications – EML and EMLc

Cancer medicines for children – new indications ATC Code: various

Proposal

Addition of new indications for currently listed cancer medicines on the EMLc.

Medicine	Indication(s)
Carboplatin	Nephroblastoma, ovarian and testicular germ cell tumours
Cyclophosphamide	Nephroblastoma
Dactinomycin	Ewing sarcoma
Dexamethasone	Burkitt lymphoma
Etoposide	Acute myeloid leukaemia, nephroblastoma, osteosarcoma
Hydrocortisone	Burkitt lymphoma
Ifosfamide	Burkitt lymphoma, nephroblastoma
Imatinib	Acute lymphoblastic leukaemia
Irinotecan	Nephroblastoma, rhabdomyosarcoma
Methotrexate	Burkitt lymphoma
Methylprednisolone	Burkitt lymphoma

Applicant

European Society for Paediatric Oncology (SIOP Europe)

WHO technical department

Noncommunicable Diseases

EML/EMLc

EMLc

Section

8.2.1 Cytotoxic medicines
8.2.2 Targeted therapies
8.2.4 Hormones and antihormones

Dose form(s) & strength(s)

Dose forms and strengths currently included in the EMLc

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The proposed medicines are all included on the EMLc for other cancer indications.

Public health relevance (burden of disease)

Cancer is a leading cause of death in children globally; the most common cancer types in children are leukaemias, lymphomas and central nervous system tumours (*1*). Childhood cancers generally cannot be prevented or screened for, so improving outcomes for children with cancer relies on early and accurate diagnosis and access to effective treatments. In 2018, WHO launched the Global Initiative for Childhood Cancer, to provide leadership and technical assistance to Member States to build and sustain high-quality childhood cancer programmes. The goal of this initiative is to achieve at least 60% survival for all children with cancer globally by 2030 (*2*).

Summary of evidence: benefits (from the application)

Cancer in children and adolescents is almost exclusively treated according to national and international treatment protocols. This is the case for first treatment and relapsed and refractory disease. Treatment regimens are devised by clinical experts from relevant tumour groups and are further developments of previous regimens. Often these treatment protocols consist of the standard arm that has proven to be effective based on previous experimental trials. All medicines proposed in this application are part of international treatment regimens and are considered the standard of care.

Acute myeloid leukaemia – etoposide

Etoposide is included in multiple trial regimens as standard therapy for children with acute myeloid leukaemia, including the AML-BFM 2012 (*3*), NOPHO-DBH AML 2012 (*4*) and ML DS 2006 (*5*) trials.

Nephroblastoma – carboplatin, cyclophosphamide, etoposide, ifosfamide, irinotecan

Carboplatin, cyclophosphamide, etoposide, ifosfamide and irinotecan are included as chemotherapy interventions along with dactinomycin, doxorubicin,

melphalan and vincristine in the SIOP 2001/GPOH (*6*) and Umbrella SIOP-RTSG 2016 (*7*) trial regimens for nephroblastoma (Wilms tumour).

Acute lymphoblastic leukaemia – imatinib

Imatinib is included in the ALLTogether trial regimen for children and young adults with acute lymphoblastic leukaemia (*8*) and the EsPhALL trial regimen for children with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (*9*).

Ewing sarcoma – dactinomycin

Dactinomycin is included in many trial regimens for Ewing sarcoma, including EICESS-92 (*10*), Euro-Ewing 2012 (*11*, *12*) and Euro-Ewing 99 (*13*, *14*) trials.

Ovarian and testicular germ cell tumours – carboplatin

Carboplatin is included in the MAKEI-V regimen for malignant extracranial germ cell tumours (*15*), and is recommended in chemotherapy regimens for extracranial germ cell tumours in children and adolescents in guidelines issued by the Children's Cancer and Leukaemia Group in the United Kingdom of Great Britain and Northern Ireland (*16*).

Burkitt lymphoma – dexamethasone, hydrocortisone, ifosfamide, methylprednisolone, methotrexate

Dexamethasone, ifosfamide and methotrexate are included in the LBL 2018 regimen for Burkitt lymphoma (*17*). Hydrocortisone, methylprednisolone and methotrexate are included in the Inter-B-NHL Ritux 2010 regimen (*18*, *19*).

Osteosarcoma – etoposide

Etoposide is included in the French OS2006 regimen for osteosarcoma (*20*, *21*).

Rhabdomyosarcoma – irinotecan

Irinotecan is included in the EpSSG FaR-RMS (*22*) and the VIT-0910 regimens for frontline or relapsed or refractory rhabdomyosarcoma (*23*, *24*).

Summary of evidence: harms (from the application)

Chemotherapy is associated with serious adverse events in the acute setting and also in the long term in cancer survivors; it therefore requires close monitoring (*25–27*). All proposed medicines in this application are already included on the EMLc. Their safety profiles are well known as a result of long-standing experience with their use.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of paediatric cancer are not available.

Burkitt lymphoma and nephroblastoma are among the six tracer cancers in the WHO Global Initiative for Childhood Cancer.

Costs/cost–effectiveness

Not reported in the application.

Availability

The proposed medicines are already included on the EMLc and are available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group advised that it supported expansion of the listings on the EMLc for the proposed cancer medicines for the proposed new indications. These medicines are all used in standard, multimodal chemotherapy protocols for the proposed indications. Expanding the EMLc indications for these medicines would support the goals of WHO Global Paediatric Cancer initiative and contribute towards the achievement of the best possible cancer care for children.

The Working Group acknowledged that the availability of clinical evidence in the paediatric context was limited but considered that obtaining the usual level of evidence required for EML listings was unlikely. In this case, efficacy and safety could be accepted based on extrapolation of the well known benefits and harms from use of these medicines in adults, for other indications in children and as part of standard cancer care in children.

Committee recommendations

The Expert Committee noted that the incidence of paediatric tumours has been steadily increasing over the past decades with the largest increases reported in youngest children.

The Expert Committee recommended the extension of the current listings on the complementary list of the EMLc of the medicines outlined in the following table for the indications specified. Noting that these paediatric cancers also affect older children and adolescents, the Committee also recommended extending the listings for these medicines on the EML.

Medicine	Indication(s)
Carboplatin	Nephroblastoma, ovarian and testicular germ cell tumours
Cyclophosphamide	Nephroblastoma

Table *continued*

Medicine	Indication(s)
Dactinomycin	Ewing sarcoma
Dexamethasone	Burkitt lymphoma
Etoposide	Acute myeloid leukaemia, nephroblastoma, osteosarcoma
Hydrocortisone	Burkitt lymphoma
Ifosfamide	Burkitt lymphoma, nephroblastoma
Imatinib	Acute lymphoblastic leukaemia
Irinotecan	Nephroblastoma, rhabdomyosarcoma
Methotrexate	Burkitt lymphoma
Methylprednisolone	Burkitt lymphoma

The Committee noted that administration of intravenous cyclophosphamide or ifosfamide required the use of the accompanying medicine mesna to prevent haemorrhagic cystitis commonly associated with these treatments. The Committee therefore also recommended the extension of the current listing for mesna on the EML and EMLc to include the indications of nephroblastoma and Burkitt lymphoma.

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Cancer medicines for head and neck cancer – review – EML

Carboplatin — ATC Code: L01XA02

Proposal

The application presented an updated review of platinum-based chemotherapy for the treatment of early- and advanced-stage head and neck cancer.

Cisplatin is already included on the EML for this indication. Carboplatin is proposed for inclusion as an alternative to cisplatin.

Applicant

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WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department concurred with the conclusion that carboplatin provides similar clinical benefit to cisplatin, with a different safety profile and less toxicity. The technical department agreed that the addition of carboplatin to the EML for use in the treatment of head and neck cancer as a radiosensitizer primarily relates to patients unable to tolerate cisplatin.

EML/EMLc

EML

Section

8.2.1 Cytotoxic medicines

Dose form(s) & strength(s)

Injection 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL, 600 mg/60 mL

Core/complementary

Complementary

Individual/square box listing

EML

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

As part of the comprehensive review of cancer medicines undertaken by the Expert Committee in 2015, cisplatin was added to the complementary list of the EML for use as a radiosensitizer in treatment protocols for head and neck cancer. Compared with postoperative radiotherapy alone, the Committee considered that the benefits associated with the addition of cisplatin, in terms of local and regional control rates, disease-free survival and progression-free survival, were of clinical relevance. The Committee also considered that the use of primary combined chemotherapy with cisplatin and radiation was associated with a clinical benefit, compared with radiation alone, in patients who have unresectable tumours (*1*).

Public health relevance (burden of disease)

Head and neck cancers include many site-specific tumours, including oral cavity and oropharyngeal cancers. However, about 90% of all head and neck cancers are squamous cell carcinomas (*2*). This group of cancers accounts for 890 000 new cases and 450 000 deaths annually and is the sixth most common cancer worldwide (*3*).

Although the incidence for nasopharyngeal cancers has decreased over the past 20 years, the incidence of oropharyngeal and hypopharyngeal cancers, and lip and oral cavity cancers has increased (*4*). The incidence of head and neck cancer varies markedly by geographical location; it is noticeably more frequent in South Asia and less frequent in western sub-Saharan Africa and Andean Latin America (*4*, *5*).

The prognosis of head and neck cancers depends largely on the location of the tumour and its stage. Overall, the 5-year survival is 66.9%. However, localized stages have a 5-year survival ranging from 62% to 96% depending of the anatomic site, while metastatic disease has a 5-year survival in the range of 20–40% (*6*).

Summary of evidence: benefits (from the application)

The applicants conducted a literature search for randomized controlled trials and systematic reviews of platinum-based chemotherapy for head and neck cancer, and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool, and judgements about precision,

consistency, directness and likelihood of publication bias were made following the GRADE approach.

Seventeen systematic reviews (used to identify relevant studies) were identified (*7–23*). No new trial evidence was found since the 2015 application.

Eight trials, in seven publications, provided data to estimate the effect of cisplatin or carboplatin on overall survival. Six trials assessed the effect of cisplatin (*24–28*), while two evaluated carboplatin (*29*, *30*). In almost all of the trials, platinum chemotherapy was used as a single chemotherapy agent; in one trial, it was used in combination with 5-fluorouracil (*30*). Participants in most of the trials had locally advanced disease.

The meta-analysis showed that the addition of cisplatin or carboplatin to radiotherapy may increase overall survival by 2 months (hazard ratio (HR) 0.95, 95% (confidence interval (CI) 0.80 to 1.12; low-certainty evidence).

Summary of evidence: harms (from the application)

Twenty-six trials reporting data on adverse events were identified from the systematic reviews and included in the meta-analysis. The addition cisplatin or carboplatin to radiotherapy may increase the risk of adverse events (risk ratio (RR) 1.16, 95% CI 1.01 to 1.16; low-certainty evidence). In absolute terms, 52 more patients per 1000 experience adverse events. The most common adverse events were mucositis, skin toxicity, dysphagia and stomatitis.

Additional evidence (not in the application)

A meta-analysis of 93 randomized trials (17 346 participants) provides a comprehensive evaluation of the effect of chemotherapies in locally advanced head and neck cancer (*31*). The meta-analysis showed that chemotherapy, when compared with radiotherapy alone, was associated with a relevant benefit in overall survival, with about 4.5% more patients being alive at 5 years (absolute improvement). This benefit was larger for concomitant chemotherapy, whereas the observed benefit for induction and adjuvant chemotherapies was uncertain. Among chemotherapies, concurrent high-dose cisplatin (100 mg/m^2 on days 1, 22 and 43 during radiotherapy) was the most effective regimen compared with 5-fluorouracil and carboplatin. Based on these results, concurrent chemoradiotherapy with cisplatin became the preferred choice for the treatment of patients with locoregionally advanced squamous cell carcinoma of the head and neck in the clinical practice guidelines of the European Head and Neck Society, the European Society of Medical Oncology and European Society for Radiotherapy and Oncology, and the National Comprehensive Cancer Network (*32*, *33*).

However, platinum-based concomitant chemoradiotherapy has acute and late toxic effects. Adding cisplatin to radiotherapy is associated with acute gastrointestinal, haematological, neurological and renal adverse effects. This

toxicity adds to the toxicity caused by radiotherapy. In randomized controlled trials, the addition of high-dose cisplatin doubled the number of cases of severe acute mucositis (*34*). More than one third of patients developed severe acute dysphagia (*35*). Severe adverse effects are also associated with decreased compliance, with a relevant proportion of patients (up to a third) unable to receive all planned cycles of chemotherapy (*34*, *36*). Late toxicity is also extremely problematic when cisplatin-based induction chemotherapy is followed by cisplatin-based concomitant chemoradiotherapy, as it decreases the quality of life of patients for the rest of their lives. For these reasons carboplatin is frequently used in routine clinical practice when cisplatin is not tolerated or contraindicated. Based on the above-mentioned meta-analysis, carboplatin and 5-fluorouracil are considered acceptable alternatives as they are associated with gains in survival (*31*). Carboplatin has a similar mode of action to cisplatin, but it is associated with less acute and late toxicities (e.g. ototoxicity, nephrotoxicity, neurotoxicity and emesis) (*37*, *38*). Carboplatin can be used in patients with impaired kidney function and can be easily dosed based on glomerular filtration rate (*39*).

WHO guidelines

WHO guidelines for the treatment of head and neck cancers are not available.

Costs/cost–effectiveness

No economic evaluation studies were identified.

Availability

Carboplatin has marketing approval from many national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. It is currently included on the Model List for other indications and is available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group noted that concomitant chemotherapy and radiotherapy using cisplatin or carboplatin is the standard of care for the treatment of head and neck cancers. Both agents are effective radiosensitizers, cisplatin is more active, but also more toxic than carboplatin. The available evidence suggests that there are no significant differences between agents in terms of survival.

The Working Group therefore advised that it supported the inclusion of carboplatin on the Model List as an alternative treatment option to cisplatin for concomitant chemoradiation therapy of head and neck cancers in patients unable to tolerate cisplatin.

Committee Recommendations

The Expert Committee noted that concomitant chemotherapy and radiotherapy using cisplatin or carboplatin is the standard of care for treating early-stage head and neck cancers and that both agents are effective radiosensitizers.

The evidence presented in the application evaluated overall survival and found only a limited overall survival benefit associated with the addition of cisplatin or carboplatin to radiotherapy compared with radiotherapy alone, with no significant difference between the two agents. However, the Committee noted that the most relevant outcome measure for chemoradiation is local control of the disease, for which both cisplatin and carboplatin are associated with benefit, particularly in early-stage disease. More evidence is available for cisplatin, and it is already included on the EML for head and neck cancer as a radiosensitizer. However, cisplatin is associated with relevant acute and late toxicities and cannot be used in the considerable proportion of patients who are unfit for this chemotherapy. The Committee considered that carboplatin can be an alternative option as a radiosensitizer for patients in whom cisplatin is contraindicated or not tolerated, due to its different and better tolerated toxicity profile.

The Expert Committee also acknowledged that the Cancer Working Group supported the inclusion of carboplatin on the EML as an alternative option to cisplatin for this indication.

The Expert Committee therefore recommended the inclusion of carboplatin as a radiosensitizer for head and neck cancers in patients unable to tolerate cisplatin.

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Doxorubicin for rhabdomyosarcoma – review – EML and EMLc

Doxorubicin **ATC Code: L01DB01**

Proposal

The application presented a review of evidence for doxorubicin in the treatment of rhabdomyosarcoma. Based on the findings of the review, doxorubicin was not proposed by the applicants for inclusion on the Model Lists for this indication.

Applicant

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WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical unit advised that in line with the recommendation from the EML Cancer Medicines Working Group, the inclusion of doxorubicin in the EMLc for rhabdomyosarcoma is justified given that it addresses a cancer type of public health relevance (rhabdomyosarcoma is the most frequent soft tissue sarcoma in children) and has potential benefits as it is more feasible for use where health systems are weak (where standard chemotherapy regimens are not available or accessible).

EML/EMLc

EML and EMLc

Section

8.2.1 Cytotoxic medicines

Dose form(s) & strength(s)

Powder for injection: 10 mg, 50 mg (hydrochloride) in vial

Core/complementary

Complementary

Individual / Square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Doxorubicin has been included on the EML and EMLc since the first editions of the lists in 1977 and 2007, respectively. The currently endorsed indications for doxorubicin on the Model Lists are:

- EML: acute lymphoblastic leukaemia, Burkitt lymphoma, diffuse large B-cell lymphoma, early stage breast cancer, Ewing sarcoma, follicular lymphoma, Hodgkin lymphoma, Kaposi sarcoma, metastatic breast cancer, multiple myeloma, nephroblastoma and osteosarcoma
- EMLc: acute lymphoblastic leukaemia, Burkitt lymphoma, diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, Kaposi sarcoma, nephroblastoma and osteosarcoma.

Medicines currently included on the EML and EMLc for the treatment of rhabdomyosarcoma are those recommended in the standard ifosfamide, vincristine and dactinomycin (actinomycin-D) (IVA) regimen, and vincristine, dactinomycin and cyclophosphamide (VAC) regimens. Mesna is also included for this indication to accompany the administration of ifosfamide (*1*).

Public health relevance (burden of disease)

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents, but it is a rare cancer type responsible for around 3% of all paediatric tumours (*2*). Data from the Surveillance, Epidemiology, and End Results (SEER) Program were used to determine incidence of rhabdomyosarcoma in the United States from 1975 to 2005. Investigators estimated an incidence of 4.4 cases per million children/adolescents a year (*3*). Rhabdomyosarcoma is divided into six histological groups with different prognoses. Pleomorphic and alveolar rhabdomyosarcoma have the worst overall survival with a 5-year survival of 26.6% and 28.9%, respectively, while embryonal rhabdomyosarcoma has the highest 5-year survival rate (73.9%) (*2*).

Summary of evidence: benefits (from the application)

Doxorubicin was considered an effective therapeutic option as a single agent for treatment of rhabdomyosarcoma before the IVA and VAC chemotherapy combinations became the standard of care. With the addition of more medicines,

e.g. ifosfamide, in the combinations, the role of doxorubicin and its contribution to overall survival have become less certain (*4*, *5*).

A multicentre, open-label, phase III randomized controlled trial evaluated the addition of doxorubicin to standard IVA chemotherapy in 484 patients with rhabdomyosarcoma aged between 6 months and 21 years (*6*). Median follow-up was 63.9 months and during this period neither median overall survival nor median progression-free survival was reached. The 3-year overall survival was 78.3% in the doxorubicin plus IVA group compared with 80.6% in the IVA group (hazard ratio (HR) 1.17, 95% confidence interval (CI) 0.82 to 1.67). The 3-year event-free survival was 67.5% in the doxorubicin plus IVA group compared with 63.3% in the IVA group (HR 0.87, 95% CI 0.65 to 1.16). Overall, the addition of doxorubicin to IVA chemotherapy did not show statistically significant improvements in outcomes, and may decrease overall survival (low-certainty evidence).

Summary of evidence: harms (from the application)

From the safety analysis of the randomized trial (*6*), the use of doxorubicin plus IVA was associated with an increased risk of adverse events, including neutropenia (risk ratio (RR) 1.03, 95% CI 0.98 to 1.09) and infections (RR 1.41, 95% CI 1.24 to 1.61). Grade 3 or 4 leukopenia, anaemia, thrombocytopenia and gastrointestinal adverse events were significantly more common in the doxorubicin plus IVA group than the IVA group.

Additional evidence (not in the application)

A 1977 study evaluated the dose response of doxorubicin in different tumour types. For non-metastatic rhabdomyosarcoma, single-agent doxorubicin produced a tumour response (i.e. reduction in tumour volume) in about 50% of patients. However, the duration of response was limited, with most patients experiencing disease progression after about 3 months (*7*).

WHO guidelines

WHO guidelines for the treatment of rhabdomyosarcoma are not available.

Costs/cost–effectiveness

No economic evaluation studies were identified.

Availability

Doxorubicin has marketing approval from many national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and United States Food and Drug Administration. It is currently

included on the Model List for other indications and is available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group noted that the addition of doxorubicin to standard chemotherapy for non-metastatic rhabdomyosarcoma was not associated with increased survival benefit and was associated with increased harms. For this reason, it was not proposed for inclusion on the Model Lists by the applicants.

However, the Working Group also considered that single-agent doxorubicin is nevertheless an effective treatment option for non-metastatic rhabdomyosarcoma and may have a place in cases where standard chemotherapy regimens are not available. As such, it was considered a valuable treatment alternative.

Therefore, the Working Group advised that it supported the inclusion of doxorubicin on the Model Lists for use as a single agent in the treatment of rhabdomyosarcoma when standard chemotherapy regimens (IVA and VAC) are not available and/or affordable.

Committee recommendations

The Expert Committee noted that doxorubicin when added to standard triplet chemotherapy (e.g. IVA and VAC) in patients with rhabdomyosarcoma at high risk of relapse was not associated with increased survival benefit but was associated with increased toxicity. Severe leukopenia, anaemia, gastrointestinal adverse events and infections were more common when doxorubicin was added to combination chemotherapy (e.g. IVA and VAC).

The Committee also noted that doxorubicin was also associated with important cardiotoxicity, especially in children. Therefore, cardiac function has to be evaluated at baseline and at intervals during treatment.

In addition, the Committee noted that tumour responses associated with doxorubicin used as a single agent were usually short-lived.

The Committee considered that the benefit-to-risk ratio of doxorubicin was not favourable in both low- and high-risk patients, and therefore did not recommend the addition of doxorubicin to the complementary list of the EML or EMLc for the new indication of metastatic or non-metastatic rhabdomyosarcoma.

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Vinorelbine – new indication – EML and EMLc

Vinorelbine **ATC Code: L01CA04**

Proposal

Inclusion of vinorelbine on the EML and EMLc for the treatment of rhabdomyosarcoma in children and adolescents.

Applicant

European Society for Paediatric Oncology (SIOP Europe)

WHO technical department

Comments were received from the WHO Department Noncommunicable Diseases. The technical unit advised that it supported the inclusion of vinorelbine on the Model Lists for the new indication of rhabdomyosarcoma. Its inclusion would also be in line with the WHO Global Initiative for Childhood Cancer that seeks to improve childhood cancer patient survival by up to 60% by 2030, with access to essential medicines as a main foundation of the initiative. The unit highlighted that consideration should be given to patient selection (high-risk disease) and capacity for toxicity management (haematological and infections rate).

EML/EMLc

EML and EMLc

Section

8.2.1 Cytotoxic medicines

Dose form(s) & strength(s)

Capsule: 20 mg, 30 mg, 80 mg
Injection: 10 mg/mL in 1 mL vial; 50 mg/5 mL in 5 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

A comprehensive review of treatment protocols for rhabdomyosarcoma was considered by the Expert Committee in 2015. The Committee noted that the use

of multidrug chemotherapy regimens comprising vincristine, dactinomycin and cyclophosphamide (VAC) and ifosfamide, vincristine and dactinomycin (IVA), in conjunction with local control measures for the primary tumour, was associated with survival rates of around 70%. The Committee recommended the inclusion of these medicines, along with the cytoprotectant mesna (to be administered with ifosfamide) on the EMLc. As rhabdomyosarcoma also affects children older than 12 years and adolescents, the same medicines were also recommended for inclusion on the EML for this indication (*1*).

Vinorelbine injection is currently included on the EML for use as part of chemotherapy protocols for the treatment of non-small-cell lung cancer and metastatic breast cancer in adults.

Public health relevance (burden of disease)

Soft tissue sarcomas are the fourth biggest group of malignancies in children after leukaemias/lymphomas, brain tumours and bone sarcomas. They account for about 7.4% of all paediatric malignancies. Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents, accounting for 3% of all paediatric cancers (*2*). The incidence is greatest in people younger than 20 years, with an incidence of 4.4 cases per million a year. The incidence decreases with age, with rhabdomyosarcoma responsible for 1% of solid cancers in adults (*3*).

Rhabdomyosarcomas are divided into four main subtypes: embryonal, alveolar, pleomorphic and sclerosing/spindle cell (*4*–*6*). Embryonal and alveolar are the two most common subtypes of rhabdomyosarcomas with frequencies of 60–70% and 20%, respectively (*6*). The outcome for children with embryonal rhabdomyosarcoma is much more favourable than the outcome for children with alveolar rhabdomyosarcoma (5-year event free survival 73% versus 29%) (*7*).

Patients newly diagnosed with rhabdomyosarcoma are assigned to a risk group that takes into account fusion status, clinical group (based on Intergroup Rhabdomyosarcoma Studies), site, nodal stage, tumour size and patient age. Treatment is subsequently adapted to risk groups.

The prognosis for paediatric patients with high-risk and metastatic rhabdomyosarcoma is still unsatisfactory. In a pooled analysis of 788 patients with metastatic (high-risk) rhabdomyosarcoma, treated with multiagent chemotherapy regimens (VAC), VAC with addition of doxorubicin and cisplatin, or VAC with addition of doxorubicin, cisplatin and etoposide, the 3-year event-free survival rate was 34% and the 3-year overall survival rate was 27% (*8*).

Summary of evidence: benefits (from the application)

A pilot study was conducted to define the optimal dose of vinorelbine when used in combination with oral low-dose cyclophosphamide in 18 children with high-risk refractory or recurrent sarcoma who had received prior induction therapy (*9*). Vinorelbine was administered at a dose of 25 mg/m^2. Overall, seven objective

responses to treatment were observed (one complete remission and six partial remissions). Three of the eight assessable patients with rhabdomyosarcoma had responses to treatment.

Combination therapy with oral cyclophosphamide and intravenous vinorelbine as maintenance treatment was evaluated as part of a multicentre, open-label, randomized, controlled phase III trial in 371 patients aged 6 months to 21 years with non-metastatic, high-risk rhabdomyosarcoma (*10*). After completion of standard treatment (nine cycles of ifosfamide, vincristine, dactinomycin with or without doxorubicin, and surgery and radiotherapy), patients in remission were randomly assigned to either stop treatment (n = 185) or to continue maintenance chemotherapy (n = 186) with six cycles of intravenous vinorelbine 25 mg/m² (days 1, 8 and 15) and daily oral cyclophosphamide 25 mg/m² (days 1–28). Median follow-up was 60.3 months.

The 5-year disease-free survival rates were 77.6% with maintenance chemotherapy versus 69.8% without (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.45 to 1.02). The 5-year overall survival rates were 86.5% with maintenance chemotherapy versus 73.7% without (HR 0.52, 95% CI 0.32 to 0.86).

The addition of vinorelbine 25 mg/m² to standard IVA chemotherapy (the so-called VIVA regimen) for patients with high-risk metastatic rhabdomyosarcoma was subsequently evaluated in a small prospective study (*11*). Preliminary results reported that after three cycles, a major partial response was seen in four (of four) cases on radiological assessment. All four patients remained alive after a median follow-up of 11 months, two in radiological complete remission and two in partial remission.

Summary of evidence: harms (from the application)

In the multicentre, phase III study, haematological toxicities and infections were the most commonly reported adverse events among patients in the maintenance chemotherapy group (*10*). Grade 4 neutropenia was the most commonly reported event (45% of patients), followed by grade 3 infection (31%). Grade 3–4 leukopenia was reported in 75% of patients and grade 3–4 neutropenia in 82%. Two serious treatment-related adverse events occurred, one case of inappropriate antidiuretic hormone secretion which resolved with treatment discontinuation, and one case of severe steppage gait with limb pain which resolved without treatment discontinuation.

In the VIVA regimen study, grade 4 neutropenia occurred in all four study participants (*11*). Grade 3 anaemia, requiring red blood cell transfusion, occurred in two patients. Infection or febrile neutropenia requiring intravenous antibiotics was seen in two patients. No grade 3 or 4 non-haematological toxicity was reported.

In general, toxicities associated with vinorelbine are well known and manageable and overall tolerance is acceptable.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of rhabdomyosarcoma are not available.

Costs/cost–effectiveness

The application estimates that one vial of generic intravenous vinorelbine 50 mg/5 mL costs between € 120 and € 150. At the recommended dose of 25 mg/m², six cycles of treatment for a child with body surface area of 1 m² would cost € 1350.

No cost information was presented for the oral vinorelbine formulation.

Availability

Intravenous vinorelbine formulations are widely available in generic brands. A generic brand of oral vinorelbine was launched in European markets in 2019.

Intravenous vinorelbine has been included on the EML since 2015, and is included on numerous national essential medicines lists globally.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the addition of oral and intravenous vinorelbine to the EMLc for the maintenance treatment of rhabdomyosarcoma. Vinorelbine, used in combination with oral cyclophosphamide, has relevant survival benefits in children with rhabdomyosarcoma, with a manageable toxicity profile. The Working Group noted that the use of vinorelbine in rhabdomyosarcoma is now established in current European and American treatment protocols and is considered the standard of care.

Noting that rhabdomyosarcoma also affects older children and adolescents, the Working Group also supported the inclusion of vinorelbine on the EML for this indication and age group.

Committee recommendations

The Expert Committee noted that maintenance treatment with oral and intravenous vinorelbine in combination with oral cyclophosphamide was associated with relevant survival benefits in children with rhabdomyosarcoma at high risk of relapse in a randomized clinical trial. Although maintenance treatment for 6 months after induction chemotherapy was associated with more

severe toxicity, the overall benefit-to-risk profile of vinorelbine was favourable, with limited related costs.

The Committee therefore recommended the addition vinorelbine on the complementary list of the EML and EMLc for the treatment of rhabdomyosarcoma in children and adolescents at high risk of relapse.

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8.2.2 Targeted therapies

BRAF/MEK inhibitors – addition – EML

Dabrafenib and trametinib	**ATC Code: L01EC02 and L01EE01**
Encorafenib and binimetinib	**ATC Code: L01EC03 and L01EE03**
Vemurafenib and cobimetinib	**ATC Code: L01EC01 and L01EE02**

Proposal

Addition of the BRAF/MEK inhibitor combinations of dabrafenib and trametinib, encorafenib and binimetinib, and vemurafenib and cobimetinib on the complementary list of the EML for use in combination for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.

Applicant

European Society for Medical Oncology (ESMO)

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that given comparisons to immunotherapy for melanoma already included on the Model List since 2019, the balance does not strongly favour adopting the class of combination BRAF/MEK inhibitors at this time.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Dabrafenib: capsule 50 mg, 75 mg/Trametinib: tablet 0.5 mg, 2 mg
Encorafenib: capsule 50 mg, 75 mg/Binimetinib: tablet 15 mg
Vemurafenib: tablet 240 mg/Cobimetinib: tablet 20 mg

Core/complementary

Complementary

Individual/square box listing

Square box, with dabrafenib and trametinib as the representative medicines, with encorafenib and vemurafenib as therapeutic alternatives to dabrafenib, and binimetinib and cobimetinib as therapeutic alternatives to trametinib.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

BRAF/MEK inhibitors have not previously been considered for inclusion on the EML.

In 2019, the Expert Committee recommended the addition of the PD-1 immune checkpoint inhibitors nivolumab and pembrolizumab to the complementary list of the EML for use as first-line monotherapy for treatment of patients with unresectable and metastatic melanoma, on the basis of evidence of significantly increased overall survival and in the absence of other EML-listed treatment options for this indication. Nivolumab was listed with a square box, with pembrolizumab specified as a therapeutic alternative (*1*).

Public health relevance (burden of disease)

The global incidence of melanoma is increasing (*2*). By 2020, the number of newly diagnosed cases of melanoma worldwide was expected to reach almost 280 000 with an estimated 68 000 deaths (*2*). As a cancer related to the exposure of the skin to sunlight, melanoma has greater variation in incidence rates across different ethnic groups and is more commonly found in fair-skinned populations of European ancestry (*3*). The global age-standardized incidence rate of melanoma is 3.4 per 100 000 persons a year, but it is much higher in Australia, New Zealand, Europe and North America than in African and Asian countries.

About 40–60% of cutaneous melanomas have mutations in the *BRAF* oncogene encoding a serine/threonine protein kinase called B-Raf which is involved in the regulation of cell division. The most commonly observed *BRAF* mutation is V600E (valine [V] is substituted by glutamic acid [E] at amino acid 600), which accounts for about 90% of the mutations in the *BRAF* gene seen in melanoma (*4*). BRAF inhibitors can block the increased activity of the mutated B-Raf kinase; however, development of resistance is common when BRAF inhibitors are used as monotherapy. For this reason, they are combined with MEK inhibitors that block the downstream mitogen-activated protein kinase pathway.

Melanoma patients with BRAF V600 mutated melanoma can be treated with PD-1 blocking immunotherapy, which is indicated for use in both BRAF mutated and wild-type melanoma. Although there are no direct comparisons of BRAF/MEK inhibitors with immunotherapy, meta-analyses suggest that while patients treated with BRAF/MEK inhibitors may have better progression-free survival, overall survival may be better in patients treated with immune checkpoint inhibitors (*5*–*7*). Targeted therapy may be preferred in patients who require a fast response, such as those with higher tumour volume, symptomatic disease, a high risk of organ or function deterioration due to metastases, and in patients in whom immunotherapy is unsuitable (e.g. patients with severe autoimmune diseases).

As mentioned before, BRAF inhibitor monotherapy for advanced BRAF-mutated melanoma has been shown to induce high response rates but

is followed shortly afterwards by resistance (*8–10*). The use of BRAF inhibitors in combination with MEK inhibitors serves to overcome the issue of resistance and the short duration of response with BRAF inhibitor monotherapy (*11*). Monotherapy with BRAF inhibitors is no longer the standard of care in advanced melanoma since the combination of BRAF/MEK inhibitors improved both progression-free survival and overall survival compared with BRAF inhibitor monotherapy (*12–14*). Monotherapy with BRAF inhibitors should be used only if an absolute contraindication for MEK inhibitors exists (*4*).

Summary of evidence: benefits (from the application)

The combined use of BRAF and MEK inhibitors has been investigated in randomized phase III trials and compared with BRAF inhibitor monotherapy and showed improved survival outcomes in BRAF V600 mutated melanoma.

Dabrafenib/trametinib

COMBI-d and COMBI-v were double-blind, randomized, phase III studies comparing dabrafenib/trametinib versus dabrafenib monotherapy or versus vemurafenib monotherapy, respectively, as first-line treatment of BRAF V600 mutated metastatic melanoma (*13*, *15*, *16*). In COMBI-d, after more than 3 years of follow-up, median overall survival in patients receiving combination therapy was 25.1 months (versus 18.7 with monotherapy), median progression-free survival was 11.0 months (versus 8.8 months with monotherapy), and overall response rate was 69%. In COMBI-v, after 23 months follow-up, median overall survival was 26.1 months in patients receiving dabrafenib/trametinib, median progression-free survival was 12.1 months and the overall response rate was 68% (18% complete response).

A pooled analysis of these studies evaluated patient survival after a median follow-up of 5 years and found the overall survival rate was 34%. A complete response was observed in 19% of the patients and, in this subgroup, the 5-year overall survival rate was 71% (*17*).

Based on results of the COMBI-d and COMBI-v studies, dabrafenib/trametinib received scores of 4 and 5 on the European Society for Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 for first line treatment of unresectable or metastatic melanoma with the BRAF V600E mutation (*18*).

Encorafenib/binimetinib

The COLUMBUS study was a two-part randomized, open-label phase III study comparing encorafenib/binimetinib with vemurafenib or encorafenib as monotherapy in patients with unresectable or metastatic melanoma with BRAF V600 mutation who were treatment naïve, or had progressed following first-line immunotherapy. After 36.8 months follow-up, median overall survival was

33.6 months with the combination treatment versus 16.9 months for vemurafenib monotherapy. Median progression-free survival for the combination treatment was 14.9 months and the overall response rate was 64% (*19*, *20*).

Based on results of the COLOMBUS study, encorafenib/binimetinib received a score of 4 on the ESMO-MCBS v1.1 for treatment of unresectable or metastatic melanoma with the BRAF V600E or BRAF V600K mutation (*18*).

Vemurafenib/cobimetinib

The coBRIM trial was a double-blind, randomized, placebo-controlled study comparing vemurafenib/cobimetinib with vemurafenib monotherapy as first-line treatment of BRAF V600 mutated unresectable or metastatic melanoma (*21*, *22*). After a median follow-up of 18.5 months, median overall survival was 22.5 months for the combination treatment compared with 17.4 months for vemurafenib monotherapy, median progression-free survival was 12.3 months versus 7.2 months and the overall response rate was 70% for the combination treatment.

Based on results of the coBRIM study, vemurafenib/cobimetinib received a score of 4 on the ESMO-MCBS v1.1 for first-line treatment of unresectable or metastatic melanoma with the BRAF V600E mutation (*18*).

No direct comparisons of the different combinations are available. An indirect analysis comparing all three combinations showed a non-significant risk reduction in progression and death in the subgroup of patients with elevated baseline lactate dehydrogenase (a well known negative prognostic marker (*23*)) receiving vemurafenib/cobimetinib compared with dabrafenib/trametinib and encorafenib/binimetinib. Therefore, in this subgroup of patients, the combination of vemurafenib/cobimetinib might be preferred (*24*).

Targeted therapy in patients with melanoma brain metastases

Melanoma brain metastases pose a particular therapeutic challenge and patients with this disease have a worse prognosis than other stage IV cancer patients (*25*). The studies evaluating systemic therapy in patients with advanced melanoma have systematically excluded patients with brain metastases. Trials specifically investigating immunotherapy and targeted therapy in patients with melanoma brain metastases have shown that these therapies are also effective intracranially. The intracranial response rate is similar to the extracranial response (*26*–*29*). There is currently evidence that PD-1-based immunotherapy, particularly combination immunotherapy with nivolumab and ipilimumab, might be more effective than BRAF/MEK inhibitors in treatment of melanoma brain metastases (*5*, *30*).

The COMBI-MB trial evaluated dabrafenib plus trametinib in patients with BRAF-mutant melanoma brain metastases (*28*). The primary and secondary endpoints were the investigator-assessed intracranial response. Preliminary

data suggest that subgroups of patients with BRAF V600 mutated melanoma with asymptomatic melanoma brain metastases who had received previous local brain therapy have better progression-free survival and overall survival than other subgroups. According to ESMO recommendations, targeted therapy is preferred to immunotherapy in patients with melanoma brain metastases who have continuous dependency on corticosteroids (> 10 mg prednisolone or equivalent) at the start of systemic treatment (*31*).

Treatment sequence

Patients with BRAF V600 mutated melanoma can receive treatment with both targeted therapy and immunotherapy. However, the optimal sequence of therapy is not defined as there are no randomized controlled trials with direct comparisons. In the first-line setting, patients treated with targeted therapy seem to respond better during the first 12 months and when progression-free survival is evaluated, with immunotherapy showing a survival benefit after the first 12 months. In the second-line setting, data indicate that targeted therapy may provide greater benefit. Clinical trials evaluating the optimal therapeutic sequence of targeted and immunotherapy are ongoing (*32*).

Summary of evidence: harms (from the application)

The frequency of adverse events with the three available combinations of BRAF/MEK inhibitors is similar (*33*). However, the type of adverse event differs and this frequently leads to choosing one or the other combination in clinical practice.

Dabrafenib induces almost no photosensitivity compared with vemurafenib, where it has been reported in 41% of patients. Dabrafenib might be a preferred treatment choice for patients living in countries with high solar exposure. Dabrafenib is also associated with fewer keratoacanthomas and squamous cell carcinomas than vemurafenib (7% versus 20–30%). The most commonly reported adverse events with vemurafenib include arthralgia (56%), fatigue (46%) and rash (41%) (*8*, *34*). Pyrexia is the most common adverse event associated with dabrafenib treatment, seen in almost half of patients treated, and this often leads to (temporary) treatment interruption (*33*, *35*). For encorafenib/binimetinib, the most frequently reported adverse events are gastrointestinal (28–40%). Cutaneous adverse events were manageable, similar to dabrafenib/trametinib and lower than for vemurafenib/cobimetinib (*19*).

Treatment with MEK inhibitors is associated with ophthalmological toxicity (such as uveitis, conjunctivitis, dry eyes), which is a class effect and typically requires treatment delay and/or suspension. The frequency of surveillance for ocular events is not uniform and depends on the MEK inhibitor type used (*36–38*). Regular ophthalmological evaluations might be useful for asymptomatic patients and are mandatory in cases of visual disturbances to identify potential complications of retinal vein occlusion such as macular

oedema, decreased visual function, neovascularization and glaucoma. Patients with a previous history of ophthalmological problems should be evaluated before the start of treatment (*39*).

Treatment with MEK inhibitors, alone or in combination with BRAF inhibitors, is associated with cardiomyopathy. Decreased left ventricular ejection fraction (LVEF) was found in 4–9% of the patients in trials evaluating treatment with targeted therapy (*12*, *13*, *40*, *41*). Patients should have a cardiological assessment, particularly assessment of left ventricular ejection fraction by echocardiogram or a multigated acquisition scan before therapy initiation, after 1 month and at 2- to 3-month intervals while on treatment. A decrease in left ventricular ejection fraction is usually managed with treatment interruption, dose reduction or discontinuation. Rarely, QTc prolongation is observed with vemurafenib therapy, but not with MEK inhibitor monotherapy. In patients with QTc > 500 ms, long QT syndrome and/or being treated with medicines known to prolong the QT interval, treatment with vemurafenib is not recommended.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of metastatic melanoma are not available.

The ESMO guidelines (*4*) and the guidelines of the United States National Comprehensive Cancer Network (*42*) include BRAF/MEK combinations among the preferred regimens for first-line treatment of unresectable or metastatic melanoma with BRAF V600 activating mutations.

Costs/cost–effectiveness

An economic evaluation of the systemic treatments for advanced melanoma that included vemurafenib/cobimetinib, dabrafenib/trametinib, ipilimumab, pembrolizumab, nivolumab and nivolumab/ipilimumab has shown that the targeted combinations were not cost-effective at current prices (often more than US$ 10 000 per month of treatment) in any jurisdiction (*43*). However, it was noted that a large number of patients treated in the real-life setting do not meet the criteria for inclusion in clinical trials (*44*, *45*). The exact cost–effectiveness in a real-world setting has not been established and reimbursement decisions have involved price negotiations or managed entry agreements with national authorities. Globally, there is significant discrepancy in access to innovative therapies for metastatic melanoma, which is correlated with economic and health system performance factors (*46*). No defined treatment duration exists for targeted therapy in the advanced setting, or for patients deriving benefit (i.e. with stable disease, partial response or complete response) (*42*). In general, patients

are treated for as long as they benefit (until disease progression) or as long as the therapy is well tolerated (i.e. without unacceptable toxicity).

Targeted therapy is restricted to patients with a BRAF V600 mutation, while PD-1 based immunotherapy can be given to all patients with unresectable or metastatic melanoma (a higher number of patients). Access and costs associated with testing for the presence of BRAF V600 mutation should also be considered.

Availability

The proposed BRAF and MEK inhibitors are all patented medicines. Primary patents are in place until 2023 (binimetinib), 2024–2026 (vemurafenib), 2025 (trametinib), 2026 (cobimetinib) and 2019 (dabrafenib and encorafenib).

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of BRAF/MEK inhibitors on the EML for the treatment of metastatic melanoma. The Working Group acknowledged a relevant benefit associated with BRAF/MEK inhibitors in second-line treatment for metastatic melanoma, and that this is the main place for therapy with BRAF/MEK inhibitors for melanoma (after failure of immunotherapy). However, BRAF/MEK inhibitors could be used as first-line therapy in patients for whom immunotherapy is not suitable or in patients for whom a rapid response is required. The Working Group noted a preference to prioritize inclusion of first-line therapies on the Model List and the established role of immunotherapy in the first-line treatment for melanoma. It therefore did not support listing of BRAF/MEK inhibitors because first-line treatment with these drugs would apply to only the small subgroup of patients for whom first-line immunotherapy is not recommended or rapid response induction is required, and approval might result in their inappropriate use for patients outside this subgroup, with the associated toxicity risks and high cost.

Committee recommendations

The Expert Committee noted the increasing incidence of melanoma globally and that treatment of metastatic melanoma is complex. With the availability of an increasing number of targeted treatments, outcomes have markedly improved for patients, at least in settings where these treatments are available. Treatment of melanoma now encompasses a series of options associated with clinically important benefits such as surgery, immunotherapy, targeted inhibition of the mitogen-activated protein kinase pathway, and radiation therapy of symptomatic anatomical sites of metastases.

The Committee recalled that the 2019 recommendation to include the anti-PD-1 receptor monoclonal antibodies nivolumab and pembrolizumab on

the EML for the treatment of metastatic melanoma was based on survival data from several phase III randomized controlled trials, which suggested that about 50% of patients with advanced melanoma receiving immunotherapies are alive at 5 years (historically 5-year survival rates were very low). However, responses to immunotherapy may develop slowly and patients may have a transient worsening of disease before the disease stabilizes or regresses. Furthermore, some patients may have contraindications to immunotherapy.

The Committee noted that BRAF/MEK inhibitor combinations are associated with meaningful gains in terms of overall survival, but the magnitude of benefit is not as large as that seen with immune checkpoint inhibitors. The Committee considered that the three combinations proposed in the application were associated with similar benefits, suggestive of a class effect. However, it was noted that the combinations have not been compared with each other in direct randomized trials.

The Committee noted that the different BRAF/MEK inhibitor combinations can vary in terms of toxicity. In real-life settings, toxicities often lead to discontinuation or dose reductions of these medicines. The Committee also noted the requirement to monitor for toxicity and adverse events in patients treated with these combinations.

The Committee considered that the optimal place in therapy for BRAF/MEK inhibitors was likely to be as second-line options in patients who fail treatment with immune checkpoint inhibitors, or as first-line options for patients with rapidly progressive disease in whom a rapid response is required.

The Committee noted the limited availability of genomic testing for identification of the BRAF V600 oncogenic driver mutation in some settings, which would be a potential barrier to access and appropriate use of BRAF/MEK inhibitors. In addition, in settings where genomic testing is unavailable or underutilized, there is a risk of unintended, harmful consequences (such as overuse of in patients who are unlikely to benefit and underuse in patients who could benefit).

Overall, the Committee considered that immune checkpoint inhibitors are still the preferred therapy for metastatic melanoma for most patients. Therefore, the Committee did not recommend listing of BRAF/MEK inhibitor combinations on the EML for the treatment of metastatic melanoma in patients with the BRAF V600 mutation.

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Cyclin-dependent kinase (CDK) 4/6 inhibitors – addition – EML

Abemaciclib	**ATC Code: L01EF03**
Palbociclib	**ATC Code: L01EF01**
Ribociclib	**ATC Code: L01EF02**

Proposal

Addition of the cyclin-dependent kinase (CDK) 4/6 inhibitors abemaciclib, palbociclib and ribociclib on the complementary list of the EML for the treatment of hormone receptor positive/human epidermal growth factor receptor negative (HR+/HER–) advanced or metastatic breast cancer.

Applicant

European Society of Medical Oncology (ESMO)

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department considered there was insufficient evidence to support the inclusion of CDK4/6 inhibitors on the EML, either as a therapeutic class or as individual medicines. It was noted that while data supported minor overall survival gains from CDK4/6 inhibitors, the magnitude of these gains may be limited and that few long-term and real-world data were available. Furthermore, the need for advanced diagnostics, the high rates of toxicity (particularly neutropenia) and high prices with uncertain cost–effectiveness were acknowledged as limitations for the use of CDK4/6 inhibitors as first-line therapy in many settings.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Abemaciclib: tablet 50 mg, 100 mg, 150 mg
Palbociclib: tablet 75 mg, 100 mg, 125 mg
Ribociclib: tablet 200 mg

Core/complementary

Complementary

Individual/square box listing

Square box, with palbociclib as the representative medicines and abemaciclib and ribociclib as therapeutic alternatives.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

CDK 4/6 inhibitors have not previously been considered for inclusion on the EML.

In 2015, as part of a comprehensive review of cancer medicines on the EML, the following medicines were endorsed for inclusion on the EML for use in protocols for the treatment of metastatic breast cancer: capecitabine, cyclophosphamide, docetaxel, doxorubicin, paclitaxel, vinorelbine, anastrozole and tamoxifen. Trastuzumab was also recommended for treatment of HER2+ early stage and metastatic breast cancer (*1*).

CDK4/6 inhibitors act on the CDK4/6 pathway which is overreactive in many breast cancers. Inhibition of the CDK4/6 pathway activates the tumour suppressor retinoblastoma-associated protein leading to cell cycle arrest.

CDK4/6 inhibitors are generally not used as monotherapy but are combined either with aromatase inhibitors or fulvestrant. Aromatase inhibitors, represented by anastrozole, are currently included in the EML. Fulvestrant is not currently included, but a separate application for listing was submitted for consideration in 2021.

Public health relevance (burden of disease)

Breast cancer is the leading cause of cancer death in women globally, responsible for 6.6% of all cancer deaths in 2018 (*2*). In high-income countries, the incidence of breast cancer is high and mortality rates are low, while in low- and middle-income countries, the incidence is lower but mortality rates are higher. The overall 5-year survival rates for high-income countries are estimated to be higher than 85%. In comparison, in low- and middle-income countries, 5-year survival rates are reported to range between 38% and 60% (*3*).

While improved early detection and advances in systemic therapy for early-stage disease have resulted in some decline in breast cancer mortality since 1989, metastatic breast cancer remains largely incurable with a median survival of about 24 months (*4*). Factors associated with poor survival include age ≥ 50 years, visceral disease, shorter disease-free interval, tumours associated with aneuploidy, tumours with a high S-phase fraction, p53 accumulation, low bcl-2 expression, negative HR status and positive HER2 status (*5*). Five-year survival for patients with metastatic disease is about 18% in Europe (*6*).

The HR+/HER2– breast cancer subtype is the most common, reported in more than two thirds of all cases (*7*).

Summary of evidence: benefits (from the application)

First-line therapy for HR+/HER2– advanced or metastatic breast cancer in pre- and postmenopausal women

Abemaciclib

MONARCH 3 was a randomized, double-blind, placebo-controlled phase III trial of abemaciclib in combination with aromatase inhibitors as initial therapy for advanced breast cancer (*8*, *9*). The trial included 493 postmenopausal women who were randomized 2:1 to abemaciclib plus a nonsteroidal aromatase inhibitor (anastrozole or letrozole according to the physician's choice) or placebo plus a nonsteroidal aromatase inhibitor. After median follow-up of 26.7 months, median investigator-assessed progression-free survival was 28.2 months in the abemaciclib arm versus 14.8 months in the placebo arm, an absolute progression-free survival gain of 13.4 months (hazard ratio (HR) 0.54, 95% confidence interval (CI) 0.42 to 0.70). Mature data for the secondary endpoint of overall survival are not yet available.

Based on results from MONARCH 3, abemaciclib received a score of 3 on the European Society for Medical Oncology magnitude of clinical benefit scale (ESMO-MCBS) v1.1 for first-line treatment in combination with an aromatase inhibitor for locally advanced or metastatic HR+/HER2– breast cancer in postmenopausal women (*10*).

Palbociclib

PALOMA 2 was a randomized, double-blind, placebo-controlled phase III trial of palbociclib in combination with letrozole as first-line therapy for advanced breast cancer (*11*). The trial included 666 postmenopausal women who were randomized 2:1 to either palbociclib plus letrozole or placebo plus letrozole. Median progression-free survival was 24.8 months in the palbociclib arm versus 14.5 months in the placebo arm, an absolute progression-free survival gain of 10.3 months (HR 0.58, 95% CI 0.46 to 0.72. Mature data for the secondary endpoint of overall survival are not yet available.

Based on results from PALOMA 2, palbociclib received a score of 3 on the ESMO-MCBS v1.1 as first-line treatment in combination with letrozole for metastatic HR+/HER2– breast cancer (*10*).

Ribociclib

MONALEESA 2 was a randomized, double-blind, placebo-controlled phase III trial of ribociclib in combination with letrozole as first-line therapy for advanced breast cancer (*12*). The trial included 668 postmenopausal women who were randomized 1:1 to either ribociclib plus letrozole or placebo plus letrozole. After median follow-up of 26.4 months, median progression-free survival was 25.3 months in the ribociclib arm versus 16.0 months in the placebo arm, an absolute

progression-free survival gain of 9.3 months (HR 0.57, 95% CI 0.46 to 0.70). Mature data for the secondary endpoint of overall survival are not yet available.

Based on results from MONALEESA 2, ribociclib received a score of 3 on the ESMO-MCBS v1.1 as first-line treatment in combination with letrozole for metastatic HR+/HER2– breast cancer in postmenopausal women (*10*).

MONALEESA 7 was a randomized, double-blind, placebo-controlled phase III trial of ribociclib plus endocrine therapy (anastrozole, letrozole or tamoxifen, each combined with goserelin) as first-line therapy for advanced breast cancer (*13*, *14*). The trial included 672 premenopausal women who were randomized 1:1 to either endocrine therapy with ribociclib or endocrine therapy with placebo. Median progression-free survival was 23.8 months in the ribociclib arm versus 13.0 months in the placebo arm, an absolute progression-free survival gain of 10.8 months (HR 0.55, 95% CI 0.44 to 0.69) (*13*). The estimated overall survival at 42 months was 70.2% in the ribociclib arm versus 46.0% in the placebo arm (HR 0.71, 95% CI 0.54 to 0.95) (*14*). An absolute gain in overall survival of 16 months for ribociclib was calculated based on the point estimate for the HR.

Based on results from MONALEESA 7, ribociclib received a score of 5 on the ESMO-MCBS v1.1 as first-line treatment in combination with endocrine therapy for metastatic HR+/HER2– breast cancer in premenopausal women (*10*).

Second-line therapy

Abemaciclib

MONARCH 2 was a randomized, double-blind, placebo-controlled phase III trial of abemaciclib in combination with fulvestrant as second-line therapy for advanced breast cancer (*15*, *16*). The trail included 669 women of any menopausal status who were randomized 2:1 to receive abemaciclib or placebo each combined with fulvestrant. After median follow-up of 19.5 months, median progression-free survival was 16.4 months in the abemaciclib arm versus 9.3 months in the placebo arm, an absolute progression-free survival gain of 7.1 months (HR 0.55, 95% CI 0.45 to 0.68) (*15*). After median follow-up of 47.7 months, median overall survival was 46.7 months in the abemaciclib arm versus 37.3 months in the placebo arm, an absolute overall survival gain of 9.4 months (HR 0.76, 95% CI 0.61 to 0.95) (*16*).

Based on results from MONARCH 2, abemaciclib received a score of 4 on the ESMO-MCBS v1.1 as second-line treatment in combination with fulvestrant for advanced HR+/HER2– breast cancer in postmenopausal women (*10*).

Palbociclib

PALOMA 3 was a randomized, double-blind, placebo-controlled phase III trial of palbociclib in combination with fulvestrant as second-line therapy for advanced breast cancer (*17*, *18*). The trail included 521 women of any

menopausal status who were randomized 2:1 to either palbociclib or placebo, each combined with fulvestrant. After median follow-up of 8.9 months, median progression-free survival was 9.5 months in the palbociclib arm versus 4.6 months in the placebo arm, an absolute progression-free survival gain of 4.9 months (HR 0.46, 95% CI 0.36 to 0.59) (*17*). After a median follow-up of 44.8 months, median overall survival was 34.9 months in the palbociclib arm versus 28.0 months in the placebo arm, an absolute gain in overall survival of 6.9 months (HR 0.81, 95% CI 0.64 to 1.03) (*18*).

Based on results from PALOMA 3, palbociclib received a score of 4 on the ESMO-MCBS v1.1 as second-line treatment in combination with fulvestrant for metastatic HR+/HER2– breast cancer (*10*).

Ribociclib

MONALEESA 3 was a randomized, double-blind, placebo-controlled phase III trial of ribociclib plus fulvestrant as first- and second-line therapy for advanced breast cancer (*19*, 20). The trial included 726 postmenopausal women who were randomized 2:1 to either ribociclib or placebo, each combined with fulvestrant. Median progression-free survival was 20.5 months in the ribociclib arm versus 12.8 months in the placebo arm, an absolute progression-free survival gain of 7.7 months (HR 0.59, 95% CI 0.48 to 0.73) (*19*). The estimated overall survival at 42 months was 57.8% in the ribociclib arm versus 45.9% in the placebo arm (HR 0.72, 95% CI 0.57 to 0.92) (*20*). An absolute gain in overall survival of 16 months for ribociclib was calculated based on the point estimate for the HR.

Based on results from MONALEESA 3, ribociclib received a score of 4 on the ESMO-MCBS v1.1 as first- or second-line treatment in combination with fulvestrant for metastatic HR+/HER2– breast cancer in postmenopausal women (*10*).

Meta-analysis of randomized controlled trials

A systematic review and meta-analysis of eight randomized controlled trials (4580 patients, of whom 2802 received palbociclib, ribociclib or abemaciclib in combination with endocrine therapy (aromatase inhibitors, tamoxifen or fulvestrant)) evaluated the efficacy of CDK4/6 inhibitors for the treatment of metastatic breast cancer and tested the heterogeneity between different compounds with regard to their effect to improve progression-free survival and overall survival (*21*). For progression-free survival, the pooled analysis showed a statistically significant improvement in patients treated with the CDK4/6 inhibitor in combination with endocrine therapy versus patients treated with endocrine therapy alone (HR 0.55, 95% CI 0.50 to 0.59). For overall survival, the pooled analysis showed a statistically significant reduction in the risk of dying in patients receiving CDK4/6 inhibitors (HR 0.76, 95% CI 0.68 to 0.85). The effect

was independent of sensitivity or not to aromatase inhibitors. Pooled analysis of data for each CDK4/6 inhibitor showed a statistically significant reduction in the risk of dying only for ribociclib and abemaciclib; for palbociclib the HR for overall survival was 0.83, 95% CI 0.68 to 1.02.

Real-world studies

The RENATA study was a prospective study of real-world use of palbociclib in combination with endocrine therapy in 128 participants (127 women, one man) of any menopausal status treated in two centres in Argentina between 2015 and 2019 (*22*). Median progression-free survival was 36.7 months with first-line treatment and 24.2 months with second-line treatment. The overall response rate was 45.3% and 25.0% in the first- and second-line setting, respectively. Median overall survival in the entire population was not reached.

Summary of evidence: harms (from the application)

The main adverse effect of the pharmacological class of CDK4/6 inhibitors is haematological toxicity. Their use is associated with a predictable, reversible and generally non-infection-prone neutropenia – related to the cell cycle effects on the haematopoiesis of the cell cycle blockade (*23*).

A systematic review and meta-analysis of the efficacy and safety of CDK4/6 inhibitors from the phase III clinical trials reported an onset of grade 3 and 4 neutropenia in 65%, 58% and 26% of patients using palbociclib, ribociclib and abemaciclib, respectively (*24*). However, the occurrence of febrile neutropenia indicating possible infection was reported in less than 1% of the trial population with any of these compounds. In general, the onset of moderate to severe neutropenia prompts a delay, temporary interruption or dose reduction of the CDK4/6 inhibitor and rarely requires other interventions due to the reversible nature of this side-effect. Granulocyte stimulating factors and/or antibiotic prophylaxis are not commonly used, as febrile neutropenia occurs quite rarely (*25*). The only precaution recommended with the use of this class of agents therefore is a complete count blood at the beginning of each cycle and, as a precaution, 2 weeks after the start of the first two cycles to check the bone marrow reserve. Moreover, CDK4/6 inhibitors are associated with molecule-specific safety profiles that informs the clinicians' decision to use one compound over another one, along with patient preference. The different safety profiles are currently the most important factor taken into account in the treatment decision for patients with HR+/HER2– advanced breast cancer in the first- or second-line of therapy, in the absence of direct comparisons. The principal differences in the safety profiles of abemaciclib, palbociclib and ribociclib from the phase III trials are summarized in Table 6.

Table 6
Adverse events in patients treated with CDK4/6 inhibitors, percentage of patients

Adverse event	Abemaciclib	Palbociclib	Ribociclib
Any grade 3 and 4 adverse event	58%	74%	79%
Grade 3 and 4 neutropenia	26%	65%	58%
Febrile neutropenia	< 1%	< 1%	< 1%
Anaemia	30% (7% grade 3)	24% (5.5% grade 3/4)	19%
Increased aspartate aminotransferase or alanine aminotransferase	All grade < 10%	All grade < 10%	25% (9% grade 3)
Diarrhoea	87% diarrhoea (13% grade 3)	25%	52%
Nausea	45% nausea (3% grade 3)	35%	35%

Treatment discontinuation was highest with abemaciclib, in part related to the higher rates of treatment-related diarrhoea (*25*).

The use of ribociclib has been associated with a prolongation of the QT-interval. An electrocardiogram finding of a QT-interval corrected for heart rate according to the Friderica formula (QTcF) > 450 ms was observed in 7% of the patients treated with ribociclib and 1% in the placebo arm (*13*, *14*, *26*). Moreover, 10% of patients receiving ribociclib experienced a QTcF prolongation of +60 ms or more in at least one postbaseline electrocardiogram assessment compared with 2% in the placebo arm. QT prolongation was more commonly observed when tamoxifen was the endocrine agent in association (16%) than when an aromatase inhibitor was used (7%). While no clinical symptoms or arrhythmias (e.g. ventricular tachycardia or torsades de pointes) were reported with the QTcF prolongation, the treatment was interrupted or reduced in 4% of the patients in the ribociclib arm, in line with the trial protocol. The United States Food and Drug Administration recommend initial electrocardiogram monitoring for patients receiving ribociclib. No potentially clinically relevant effect on the QTc interval has been reported with abemaciclib or palbociclib (*27*).

Other studies have addressed the possible differences in safety of CDK4/6 inhibitors in different ethnic populations. An analysis of real-world use

of palbociclib with endocrine therapy in patients with HR+/HER2– advanced breast cancer in Argentina found a higher rate of febrile neutropenia than observed in the phase III trials (*22*). A real-world study on the use of palbociclib in 169 patients with metastatic breast cancer in South Korea reported neutropenia (mostly grade 3 or 4) in 88.3% of patients which is higher than reported in phase III studies (*28*). Similarly, a higher incidence of haematological toxicity was reported in a phase II single-arm trial of palbociclib plus letrozole as first-line treatment in 42 postmenopausal participants with advanced breast cancer in Japan; neutropenia was reported in 100% of participants, of whom 93% had grade 3 or 4 neutropenia (*29*). Sufficient data are lacking on the haematological effects of CDK4/6 inhibitors in women of African ethnicity, in whom a high incidence of benign ethnic neutropenia has been reported (*30*, *31*).The phase II PALINA trial is evaluating the safety of palbociclib in combination with letrozole or fulvestrant in African American women; the results had not been reported at the time the application was submitted (*32*).

Additional evidence (not in the application)

Results from the PALINA trial were published in June 2021. This trial included 35 African American women with HR+/HER2– advanced breast cancer. Duffy null polymorphism, which is associated with reduced neutrophil counts in individuals of African ancestry, was present in 19 participants. Grades 3 and 4 neutropenia were observed in significantly more participants with Duffy null status compared to Duffy wild-type (72% versus 23.2%). Duffy null status was also associated with significantly lower overall mean (standard deviation) dose intensity (81.9% (15.9%) versus 95.7% (5.9%)), and a significantly lower clinical benefit rate (66.7% versus 84.6%). No cases of febrile neutropenia or permanent treatment discontinuation due to neutropenia were reported.

WHO guidelines

WHO guidelines for the treatment of breast cancer are not available.

Costs/cost–effectiveness

Many cost–effectiveness analyses have found CDK4/6 inhibitors unlikely to be cost-effective at current prices and usual willingness-to-pay thresholds.

A study in Singapore evaluated the cost–effectiveness of adding ribociclib to goserelin and an aromatase inhibitor or tamoxifen as initial therapy for premenopausal women with breast cancer, using a partitioned survival model based on the MONALEESA 7 trial (*33*). The base-case analysis resulted in an incremental cost–effectiveness ratio of Singapore $ 197 667 (about US$ 148 700 using the average 2020 exchange rate) per quality-adjusted life-year (QALY). The authors concluded that ribociclib was unlikely to be cost-effective in this setting for the approved indication.

A cost–effectiveness analysis of palbociclib or ribociclib (both plus letrozole) in the United States estimated an incremental cost–effectiveness ratio per QALY gained of US$ 634 000 for palbociclib and US$ 440 000 for ribociclib (*34*).

A Canadian cost–effectiveness analysis of ribociclib plus endocrine therapy versus endocrine therapy alone reported an incremental cost–effectiveness ratio of CA$ 197 832 per QALY gained as a best estimate (*35*). The authors had some concerns about the certainty of the cost–effectiveness estimations for the use of CDK4/6 inhibitors in first-line treatment of premenopausal women, as they were based mostly on the predicted clinical benefit beyond the actual trial follow-up.

An Italian study reported that when abemaciclib was used as first-line treatment, the estimated cost was € 2246 a month of progression-free survival gained, less expensive at full dose than ribociclib and palbociclib. In the second-line setting, in combination with fulvestrant, ribociclib was the least expensive, with an estimated cost of € 2070 a month of progression-free survival gained (*36*).

A Chinese cost–effectiveness analysis of palbociclib as second-line therapy reported an incremental cost–effectiveness ratio of US$ 182 779 per QALY. When the price of palbociclib was reduced to 30%, 20% and 10% of the current price, the resultant incremental cost–effectiveness ratios were US$ 79 558, US$ 64 812, and US$ 50 066 per QALY, respectively. To meet 50% probability of cost–effectiveness, the estimated price required was US$ 32.52/100 mg at a willingness-to-pay threshold of US$ 58 480 per QALY. The authors concluded that adding palbociclib to a fulvestrant regimen is unlikely to be cost-effective as second-line endocrine therapy for patients with HR+/HER2– metastatic breast cancer, at the current price in China (*37*).

Availability

Abemaciclib (trade name Verzenio, Eli Lilly) has regulatory approval in multiple countries globally. It has primary patent protection until 2029.

Palbociclib (trade name Ibrance, Pfizer) has regulatory approval in multiple countries globally. It has primary patent protection until 2023.

Ribociclib (trade name Kisqali, Novartis) has regulatory approval in multiple countries globally. It has primary patent protection until 2027–2029.

Generic products are not currently available.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of CDK4/6 inhibitors as a therapeutic class or as individual medicines on the EML at this time. For all the medicines proposed, the Working Group noted that long-term trial follow-up is limited, and that the survival benefit

observed is currently uncertain. A review of the data after longer follow-up could be considered for a future EML update. Based on clinical benefit, only ribociclib meets the EML criteria for first-line survival benefit and ESMO-MCBS score. However, there are concerns about bias in the MONALEESA 7 trial, including high censoring rates, which reduce confidence in the estimates of benefit. In addition, the eligible patient population for these medicines is likely to be very large, current costs are very high with cost–effectiveness analyses finding these treatments not to be cost-effective in most settings at current prices. Treatment duration is long and therefore the effect on the budget of health systems would be substantial and unaffordable in many settings.

Committee recommendations

The Expert Committee noted that breast cancer continues to be the leading cause of cancer death in women, and that more than half of women diagnosed with breast cancer have HR+/HER2– disease.

The Committee noted the results of clinical trials on CDK 4/6 inhibitors in the first- and second-line treatment settings suggest a potentially meaningful survival benefit with this class of medicines when added to endocrine therapy compared with endocrine therapy alone. However, the Committee considered that, while promising, these survival data are currently immature. In particular, in the first-line setting, it is not yet known if the progression-free survival gains seen in trials will translate to overall survival benefit in the long term.

Other areas of uncertainty identified by the Committee included questions on the optimal dose and duration of treatment, use in early-stage disease, and whether meaningful clinical differences exist between individual medicines within the pharmacological class.

The Committee also noted that CDK4/6 inhibitors are unlikely to be cost-effective in most settings at their current high prices and would pose serious affordability challenges, especially in low- and middle-income countries.

The Expert Committee therefore did not recommend the listing of CDK 4/6 inhibitors on the EML at this time. The Committee recognized that more mature survival data are likely to be available in the near future, and requested that an application with updated survival data be submitted for consideration by the Expert Committee in 2023. The Committee also considered that CDK 4/6 inhibitors could be flagged to the Medicines Patent Pool as candidates for consideration for negotiating public health-oriented licences, noting that the timelines for negotiating such licences are lengthy. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this class of medicines in low- and middle-income countries.

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Everolimus – addition – EML and EMLc

Everolimus — ATC Code: L01EG02

Proposal

Addition of everolimus to the complementary list of the EMLc for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex in children who need a therapeutic intervention but are not eligible for surgery.

Applicant

European Society for Paediatric Oncology (SIOP Europe)

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that everolimus has well established and clinically relevant efficacy for the treatment of SEGA in children. It is important to note, however, that such treatment requires specialist diagnosis (that may include use of magnetic resonance imaging (MRI) and specialized in vitro diagnostic tests such as immunohistochemistry and fluorescence in situ hybridization) and a multispecialty team for monitoring. Furthermore, SEGA is a rare condition mainly affecting children with tuberous sclerosis.

EML/EMLc

EMLc

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Tablet: 2.5 mg, 5 mg, 7.5 mg, 10 mg
Dispersible tablet: 2 mg, 3 mg, 5 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Everolimus has not previously been considered for inclusion on the EMLc.

Tuberous sclerosis complex is an autosomal dominant genetic disorder characterized by the development of hamartomas (slow-growing, benign tumours) in different organs. SEGA is a non-infiltrative, slow-growing tumour of the central nervous system occurring predominantly in patients with tuberous sclerosis complex. It is classified as a low-grade glioma corresponding to grade I brain lesions according to the WHO classification of tumours of the central nervous system (*1*).

The typical location of SEGA near the ventricles (subependymal) and the foramen of Monro (the conduit between the lateral ventricles and the third ventricle) and their tendency to grow can lead to obstructive hydrocephalus with substantial morbidity and mortality, including increased intracranial pressure, neurological deficits or deterioration in seizure control.

Tuberous sclerosis complex is caused by a mutation in the TSC1 and/or TSC2 gene. These genes are normally involved in regulating cell growth and division by controlling the activity of the mammalian target of rapamycin (mTOR) protein. Mutations in the TSC1 and/or TSC2 gene lead to an activation of the mTOR complex 1 (mTORC1), resulting in uncontrolled cell growth. Everolimus directly inhibits the mTOR pathway (*2*, *3*) and thus the uncontrolled division of cells harbouring the tuberous sclerosis complex mutation, leading to a reduction in the size of the tumour.

The alternative treatment options to everolimus are surgery and the symptomatic treatment of secondary complications, such as ventriculoperitoneal shunts (*4*, *5*).

Public health relevance (burden of disease)

Tuberous sclerosis complex is an autosomal dominant, genetic neurocutaneous disorder characterized by multisystem hamartomas, associated with neuropsychiatric features. With a prevalence of about one in 6000 newborns, tuberous sclerosis complex is a rare disease; nevertheless, nearly 1 million people are affected worldwide (*6*, *7*).

The TuberOus SClerosis (TOSCA) registry provides epidemiological data on SEGA in patients with tuberous sclerosis complex. In the TOSCA registry, SEGAs are reported in 25% of patients with tuberous sclerosis complex. The median age at diagnosis of SEGA is 8 years (range < 1–51 years), with 27% diagnosed before the age of 2 years and 82% before 18 years (*8*).

Tuberous sclerosis complex, as the underlying condition of SEGA, is a life-long condition.

Summary of evidence: benefits (from the application)

A 2007 phase I/II study assessed the effect of everolimus in 28 participants older than 3 years (median 11 years, range 3–34 years) with SEGA progression

between two MRI scans (*9*). At month 6 after the start of treatment, a ≥ 30% volume decrease of SEGAs was observed in 21 participants (nine had a reduction of ≥ 50%). The robustness and consistency of this finding were supported by the fact that the change in SEGA volume was significant when assessed by the local investigator and an independent central outcome reviewer. Everolimus also reduced clinical and subclinical seizure frequency (median change, –1 seizure, $P = 0.02$). In nine of 16 children, seizure frequency decreased, six had no change and seizure frequency increased in one child. An extension of this study showed that at month 60 after the start of treatment, 12/23 participants (52%) experienced a volume reduction of ≥ 50% and 14/23 (61%) of ≥ 30% (*10*). Both studies have the inherent limitations of including only the small number of participants and the lack of a control arm. However, the biological rationale that supports use of everolimus is strong and, for this brain tumour, volume reduction and seizure frequency can be considered clinically relevant outcomes.

The EXIST-1 trial was a multicentre, double-blinded, randomized (2:1), placebo-controlled, phase III study that evaluated the efficacy and safety of everolimus in 117 participants aged > 3 years at diagnosis of a SEGA (*11*). After a median of 9.6 months of everolimus treatment, 35% and 77% of participants experienced a > 50% and > 30% reduction in SEGA volume, respectively. At month 6, the progression-free rate was 100% for everolimus and 86% for placebo ($P < 0.001$).

An open-label extension study of EXIST-1 included 111 participants who received at least one dose of everolimus (median age at diagnosis 9.5 years; range 1.1–27.4 years) (*12*). Overall, 54 participants (49%, 95% confidence interval (CI) 39.0% to 58.3%) had a response of ≥ 50% or greater reduction in SEGA volume at least once during the study period.

The final results from the EXIST-1 trial showed that 57.7% of participants reached a SEGA volume reduction of ≥ 50% at least once during the study period (*13*). No participants needed surgery. Additional clinical benefits observed in this study included a reduction in the volume of renal angiomyolipoma of ≥ 50% in 73.2% of participants and 58.1% of participants had an improvement in skin lesions.

A case series in five infants younger than 12 months showed that treatment with everolimus was feasible in children during the first year of life. All five infants had a reduction in the SEGA volume of ≥ 50% within 6 months, with the most rapid reduction in the first 3 months (*14*).

In summary, reasonable evidence exists that everolimus treatment reduces SEGA volume. The effect on lesions at other sites (kidney, skin) and on seizure frequency is less clear, although a reduction in all these outcomes have been reported (*9*–*11*, *13*).

Summary of evidence: harms (from the application)

The most frequent adverse events of everolimus reported in the EXIST-1 trial were mouth ulceration (30%) and stomatitis (43%) of mild to moderate grade (*12*). Participants included in the open-label phase I/II study also showed upper respiratory tract infection, sinusitis, otitis media, pyrexia and acneiform dermatitis (*2*, *9*). No drug-related grade 4 or 5 events or death were reported (*9*, *11*).

In the final results of the EXIST-1 trial (*13*), 91% of participants needed at least one dose interruption or reduction, with adverse events being the most frequent reason for dose interruption (72%). Discontinuation of everolimus due to adverse events occurred in about 10% of participants in this study. One death was reported but was not suspected to be treatment-related.

In the NCT00411619 extension study (*10*), all participants needed at least one dose modification, including dose interruption, dose reduction and/or dose increase due to adverse events or because it was required by the protocol (blood concentration too low or high).

Adverse events identified in the case series describing use of everolimus in infants included infection, stomatitis and increase triglycerides (*14*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO Guidelines for the treatment of SEGA are not available nor are WHO guidelines for the treatment of low-grade glioma.

Costs/cost–effectiveness

No comparative cost–effectiveness data are available.

The application reported an annual cost of treatment for a 10-year-old child at a dosage of 5 mg everolimus a day, based on medicine prices from the Netherlands, to be € 30 436 and € 34 526 for standard tablets and dispersible tablets, respectively. However, medicine prices will vary from country to country.

Availability

Everolimus has regulatory approval from multiple national regulatory agencies for treatment of SEGA associated with tuberous sclerosis complex in patients aged 3 years and older who require therapeutic intervention but who are not candidates for curative surgery. It is available in both branded and generic forms. Everolimus also has regulatory approval for other indications including renal cell cancer, pancreatic neuroendocrine tumours, hormone-receptor-positive advanced breast cancer, and (in lower doses) for prophylaxis of organ rejection in patients receiving organ transplants.

Other considerations

For the diagnosis of SEGA, MRI must be available and neuroradiologists trained in paediatric neuroradiology are required for the interpretation of the images and clinical implications. If SEGA is detected on imaging, genetic counselling of the patient and family is necessary.

After a defined starting dose, everolimus has to be adjusted individually to reach a blood concentration of 5–15 ng/mL. Younger age at treatment (< 6 years) and concomitant treatment with drugs that induce CYP3A4 require higher starting doses. Therapeutic drug monitoring and dose titration for everolimus are required. Treatment of SEGA is guided by follow-up MRI to assess tumour volume and response to treatment.

The EML Cancer Medicines Working Group advised that it supports the inclusion of everolimus on the EMLc for the treatment of SEGA in children. If recommended by the Expert Committee, it should be very clearly communicated that the recommendation is for this indication alone, and not for other indications where the evidence for everolimus has not been reviewed. The Working Group noted that SEGA is a very rare disease with a strong genetic component. There is evidence of benefit for everolimus in the treatment of children with SEGA. However, the Working Group had some concerns about the feasibility of safe and appropriate use of everolimus in some settings, noting the requirements for specialist diagnosis and monitoring.

Committee recommendations

The Expert Committee noted that subependymal giant cell astrocytoma (SEGA) is a rare disease affecting almost exclusively children with tuberous sclerosis complex and is associated with considerable neurological morbidity and mortality. The Committee also noted that diagnosis of SEGA requires specialist paediatric neuroradiology expertise and the availability of facilities for magnetic resonance imaging, as well as multispecialty teams including oncologists and specialists in the treatment of epilepsy, which may be limited or unavailable in some settings.

SEGA management historically had few options other than surgery, as radiotherapy and chemotherapy were not effective. The Committee noted that everolimus is associated with reductions in SEGA volume and clinical and subclinical seizure frequency. Evidence of efficacy and safety is limited as the condition is rare. No studies have been done comparing everolimus with surgery, nor and there any substantive studies that report on quality of life with everolimus treatment. Regular monitoring of everolimus treatment for adverse events and toxicity is required, leading to frequent dose adjustments. In addition, the need for and high cost of frequent high-level care during treatment may make this treatment inaccessible to many low- and middle-income countries.

The Committee noted that everolimus is mainly used in patients with tuberous sclerosis complex, who are not candidates for surgery because of the location of tumours or because the disease has progressed after SEGA resection. However, everolimus has replaced surgery as first choice in several settings.

The Expert Committee acknowledged that the Cancer Working Group supported the inclusion of everolimus on the EMLc to treat SEGA in children, although the treatment requires specialist diagnosis.

Based on the available evidence, the Committee considered everolimus to have a favourable benefit-to-harm ratio, especially in patients who are not eligible for surgery or when surgery cannot remove the whole tumour.

The Expert Committee therefore recommended the inclusion of everolimus on the complementary list of the EMLc for the treatment of SEGA in children with tuberous sclerosis complex. Recognizing that SEGA is a life-long condition, the Committee also recommended inclusion of everolimus on the EML for patients older than 12 years. The Expert Committee did not endorse the use of everolimus for indications other than SEGA for which the evidence has not been reviewed.

The Committee noted that the inclusion of everolimus on the Model Lists supports the WHO Global Initiative for Childhood Cancer that seeks to improve childhood cancer patient survival to up to 60% by 2030 with access to essential medicines as a main part of the initiative.

The Committee advised the Strategic Advisory Group of Experts on In Vitro Diagnostics that everolimus should be considered as a moderate priority candidate for which therapeutic drug monitoring assays should be evaluated for inclusion on the WHO Model List of Essential In Vitro Diagnostics.

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Ibrutinib – addition – EML

Ibrutinib — ATC Code: L01EL01

Proposal

Addition of ibrutinib to the complementary list of the EML for the treatment of chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma in patients with a high risk of progressing to aggressive disease and patients with relapsed refractory chronic lymphocytic leukaemia.

Applicant

Ignacio Neumann; Department of Health Research Methods, Evidence and Impact, McMaster University, Ontario, Canada

Pamela Burdiles; Faculty of Medicine, Universidad Andrés Bello, Santiago, Chile

Paula Nahuelhual; Faculty of Clinical Medicine, Clínica Alemana de Santiago–Universidad del Desarrollo, Santiago, Chile

Eduardo Quiñelen; Department of Kinesiology, Universidad Metropolitana de Ciencias de la Educación, Santiago, Chile

Katherine Cerda; Department of Health Technology Assessment and Evidence Based Health, Ministerio de Salud de Chile, Santiago, Chile

Felipe Vera; Health Technology Assessment Unit, Clinical Research Center, Pontificia Universidad Católica de Chile

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that at the current time, there was not a strong justification for inclusion of ibrutinib on the EML. The department acknowledged that CLL with 17p/TP53 deletion could be a specific indication for which ibrutinib may have merit; however, given the important health system requirements, including the need for complex diagnostic tests (to avoid inappropriate prescribing and use), the high risk of clinically relevant side-effects, and the absence of an improvement in quality of life, the technical department concluded that there were currently insufficient data to merit its inclusion. The technical department also noted that more data on the clinical benefit of ibrutinib for the treatment of patients with CLL with 17p/TP53 deletion would be valuable to better evaluate its potential role as an essential medicine.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Ibrutinib: capsule 140 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Ibrutinib has not previously been considered for inclusion on the EML.

Medicines currently included on the EML for CLL are bendamustine, chlorambucil, cyclophosphamide, fludarabine, prednisolone and rituximab, recommended for inclusion as part of the comprehensive review of cancer medicines undertaken by the Expert Committee in 2015 (*1*).

Ibrutinib belongs to the class of Bruton tyrosine kinase inhibitors which are currently not listed on the EML for any indication. Continuous activation of Bruton tyrosine kinase plays an important role in the proliferation of malignant B-cells, which can be counteracted by Bruton tyrosine kinase inhibitors.

Public health relevance (burden of disease)

CLL is the most common form of adult leukaemia in many high-income countries and its incidence increases significantly with age (*2*). Its incidence in Australia, North America and some European countries is considerably higher than in Asian and Central and South American countries. Age-adjusted incidence rates range from 0.1 per 100 000 people in Japan for both males and females, to 2.4 per 1000 000 for females and 4.5 per 100 000 for males in Canada (*3*). Globally, the absolute number of deaths due to CLL increased by 70% from 1990 to 2017. Of note, the age-adjusted death rates have decreased in high-income regions, largely due to access to and availability of effective treatments, but have increased in many lower-income settings where effective treatment is not available or affordable (*4*).

Since CLL is a slowly progressing disease, patients with early-stage asymptomatic disease usually do not require treatment. In patients with more advanced and symptomatic disease, the aim of treatment is to improve the quality of life and prolong survival since for now, with few exceptions, CLL cannot be cured.

Patients with CLL with chromosome 17p deletion are a high-risk subgroup whose disease is refractory to chemoimmunotherapy with the treatments currently included on the EML, and whose prognosis is very poor. CLL with 17p deletion accounts for than 10% of new cases, and 30–50% of relapsed/refractory cases previously treated with chemoimmunotherapy (*5*). Ibrutinib appears to benefit in this subgroup of patients.

The economic burden of CLL on both patients and health systems is substantial. Annual direct costs per person with CLL have been estimated to range between US$ 4500 in Germany and US$ 44 000 in the United States of America (*6*).

Summary of evidence: benefits (from the application)

Four systematic reviews (*7–10*) and five randomized trials (*11–15*) assessing ibrutinib for the treatment of CLL were identified in the application. Two of these trials were direct comparisons of ibrutinib with another targeted therapy not included on the EML (another Bruton tyrosine kinase inhibitor in one study and an anti-CD20 monoclonal antibody in the other) and were therefore not included in the meta-analysis conducted by the applicants (*11*, *15*). The remaining three trials provided data on the effect of ibrutinib as a first- or second-line of treatment in patients with CLL.

Two trials were conducted in treatment-naïve patients. One compared ibrutinib with chlorambucil for 12 cycles in patients without the 17p deletion (*12*), while the other trial evaluated ibrutinib plus obinutuzumab (an anti-CD20 monoclonal antibody) versus chlorambucil plus obinutuzumab for six cycles (*13*). This trial included participants with 17p deletion, although they represented only a small proportion of the participants included (about 14%). The third trial enrolled participants with relapsed/refractory disease and assessed the effect of ibrutinib plus bendamustine and rituximab versus bendamustine plus rituximab alone. Participants with the 17p deletion were excluded from this study due to the known poor response of these patients to bendamustine plus rituximab (*14*).

A meta-analysis of these three studies showed that the use of ibrutinib as a first- or second-line treatment probably increases progression-free survival (hazard ratio (HR) 0.20, 95% confidence interval (CI) 0.14 to 0.27; high-certainty evidence) and probably also overall survival (HR 0.44, 95% CI 0.20 to 0.97; moderate-certainty evidence). Median overall survival had not been reached. Median progression-free survival was reached in one trial of patients with relapsed/refractory disease (*14*), and indicated a progression-free survival gain of 50.8 months in absolute terms.

One trial reported the effect of ibrutinib on quality of life and found that the use of ibrutinib resulted in a statistically significant improvement in scores of the Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue and the European Organization for the Research and Treatment of Cancer Quality

of Life Questionnaire (EORTC QLQ-C30) questionnaires. The mean difference observed in the FACIT – Fatigue score was 2.6 points (95% CI 0.4 to 4.9 points); however, this is below the minimally important differences reported for this scale (*16*). In addition, the mean difference reported in the physical functioning score of EORTC QLQ-C30 was 5.0 points (95% CI 0.75 to 9.25 points), which is also under the reported minimal important difference for this domain (*17*).

Summary of evidence: harms (from the application)

Only one of the included trials reported adverse events in both treatment groups (*13*). For the comparison of ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab, the frequency of grade 3 and 4 adverse events was similar in both arms (risk ratio (RR) 0.98, 95% CI 0.82 to 1.17; low-certainty evidence). Common adverse events associated with ibrutinib included neutropenia, pneumonia, hypertension, anaemia, hyponatremia and atrial fibrillation.

However, systematic reviews have linked the use of ibrutinib with an increased risk of hypertension, atrial fibrillation and major bleeding (*9*, *10*). The use of ibrutinib (in comparison with regimens without ibrutinib) probably results in 60 more cases of hypertension (95% CI 20 to 160 more; moderate-certainty evidence), 19 more cases of atrial fibrillation (95% CI 10 to 58 more; high-certainty evidence) and 122 more bleeding events (95% CI 8 fewer to 370 more; moderate-certainty evidence) per 1000 patients treated.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of CLL are not available.

Costs/cost–effectiveness

Three studies that evaluated the cost–effectiveness of ibrutinib for treatment of CLL/small lymphocytic lymphoma were identified in the application (*18–20*).

One study was a cost–utility analysis from the Swedish health system perspective in a population of patients with refractory or relapsed CLL (*18*). The authors concluded that ibrutinib could be cost-effective compared with ofatumumab, idelalisib plus ofatumumab or physicians' choice of treatment. However, the incremental cost–effectiveness ratios were around € 60 000 per quality-adjusted life-year (QALY) gained, higher than the thresholds most often used in European countries.

A cost–utility analysis from the United States Medicare perspective was done using ibrutinib as first-line therapy versus obinutuzumab and chlorambucil (*19*). In a cohort of patients older than 65 years without the 17p deletion, the incremental cost–effectiveness ratios was US$ 189 326 per QALY gained,

showing that ibrutinib was not a cost-effective alternative at the current price and willingness-to-pay thresholds.

The third study was a cost–utility analysis from the perspective of the National Health System of the United Kingdome of Great Britain and Northern Ireland in adults with untreated CLL. The model compared ibrutinib with obinutuzumab plus chlorambucil and showed an incremental cost–effectiveness ratio of £ 75 648 per QALY gained, which is more than the commonly used willingness-to-pay thresholds used in the United Kingdom of £ 20 000–30 000 per QALY gained used by the National Institute for Health and Care Excellence for new treatments, and of £ 50 000 per QALY gained for end-of-life treatments (*20*).

The applicants report that national reimbursement agencies in Australia, Canada and the United Kingdom have evaluated the cost–effectiveness of ibrutinib and recommended coverage, albeit in specific subgroups of patients and under confidential pricing agreements.

Availability

Ibrutinib has marketing approval from multiple national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. Ibrutinib is under patent until 2027. However, generics are available in some countries.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the inclusion of ibrutinib on the EML as first-line treatment for the high-risk subgroup of patients with CLL with 17p deletion, recognizing that this population has a significantly poorer prognosis, and an unmet need for effective treatment exists. A broader role for ibrutinib in all patients with CLL, and in the second-line setting, is not supported at this time.

However, the Working Group noted the significant cardiovascular toxicity associated with ibrutinib, in particular atrial fibrillation and major bleeding, management of which requires specialized care and resources that may not be widely available in some settings. The Working Group also considered that the need for molecular testing to identify patients with 17p deletion, who are most likely to benefit from treatment, may be a further limitation, particularly in some resource-constrained settings where such testing may not be available or affordable.

The Working Group also recognized the high cost of the medicine, the potentially long duration of treatment and the fact that ibrutinib has not been found to be cost-effective at current prices in multiple analyses. It is hoped

that with the emerging availability of generics in some settings, the price will decrease and treatment will be more affordable.

Committee recommendations

The Committee noted that targeted therapy with Bruton tyrosine kinase inhibitors, such as ibrutinib, was now emerging as the cornerstone of CLL treatment in high-income countries, replacing chemoimmunotherapy as the accepted standard of care because such therapy is more effective, has less acute toxicity and a minimal risk of development of secondary leukaemias.

The Committee considered the results of the meta-analysis presented in the application which covered all patients with CLL, and which showed with moderate-certainty evidence that ibrutinib increased overall survival, and with high-certainty evidence that ibrutinib increased progression-free survival. The trials included in the meta-analysis were in both the first-line and relapsed/refractory settings, and in both settings, ibrutinib was consistently associated with highly relevant clinical benefits. The Committee noted that in relapsed/refractory patients, the data were more mature (6 years of follow-up), with ibrutinib showing significantly longer overall survival and progression-free survival than immunotherapy with the anti-CD20 monoclonal antibody ofatumumab, including in patients with high-risk disease features such as 17p deletion or other genetic mutations associated with poor prognosis. In the first-line treatment setting, the available data are less mature (3 years of follow-up), but they also demonstrate benefit in terms of progression-free survival and response rates of ibrutinib compared with chemoimmunotherapy, including in patients with high-risk disease features. In absolute terms, the use of ibrutinib prolongs progression-free survival by at least 50 months compared with chemoimmunotherapy, with the effect being relatively uniform and robust in both first- and later-line settings. However, the quality of evidence supporting the use of ibrutinib in the subgroup of patients with CLL with 17p deletion is not as complete as it is for the whole population of patients with relapsed/refractory CLL and is immature for treatment-naïve patients.

With regard to safety, the Committee noted the significant cardiovascular toxicity associated with ibrutinib, particularly atrial fibrillation and hypertension. Most patients who start ibrutinib for CLL will remain on this drug for many years as treatment is usually continued until disease progression. Monitoring and management of these side-effects require considerable resources. Major bleeding is also seen in some patients, for which specialized care and resources are required for management.

The Committee considered that the data in the relapsed/refractory setting were compelling for a major sustained benefit and improved tolerability for all patients with CLL (with or without 17p deletion). Therefore, the

Committee recommended the inclusion of ibrutinib on the complementary list of the EML for the treatment of relapsed/refractory CLL.

The Committee acknowledged the potential role for ibrutinib as first-line treatment, particularly in the subgroup of patients with CLL with 17p deletion, but considered that the available evidence, while promising, was currently immature unlike the evidence for relapsed/refractory disease. The Committee therefore did not recommend listing ibrutinib for first-line treatment at this time. The Committee requested that an application be submitted for consideration at the next Expert Committee meeting when more mature data on ibrutinib for first-line treatment will be available.

The Committee noted that ibrutinib was not found to be cost-effective at current prices in multiple analyses, particularly when used in first-line treatment for all patients. The Committee recognized the very high price of ibrutinib (tens of thousands of US$ per year in many settings), and the long duration of the treatment, which will have a significant financial impact on individuals and health systems. The increasing availability of other Bruton tyrosine kinase inhibitors and the availability of generics of ibrutinib reported in a few countries were also noted, and it was expected that these factors would introduce competition to reduce prices. Nevertheless, the Committee recognized that the current price of ibrutinib was prohibitive for most low- and middle-income countries. The Committee also considered that the lack of access to molecular testing to identify CLL patients with chromosome 17p deletion may be a limitation in some resource-constrained settings. Therefore, the Committee did not limit ibrutinib treatment to this subgroup when making its recommendation.

The Committee recommended that ibrutinib be flagged to the Medicines Patent Pool as a candidate for negotiating public health-oriented licences with the patent-holding companies to facilitate more affordable access to ibrutinib in low- and middle-income countries. In addition, the Committee considered that ibrutinib would be a potential candidate for WHO prequalification to facilitate access to affordable and quality-assured products. The Committee therefore requested the WHO Prequalification Programme consider the inclusion of ibrutinib in its invitation for expressions of interest to manufacturers, so that ibrutinib can be eligible for prequalification.

Finally, recognizing the emerging important role of Bruton tyrosine kinase inhibitors as a therapeutic class in first- and second-line treatment of CLL, the Committee advised that it would welcome an application including other Bruton kinase inhibitors (e.g. acalabrutinib, zanubrutinib) for consideration as therapeutic alternatives for inclusion on the EML in the future.

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Imatinib – new indication – EML

Imatinib — ATC Code: L01EA01

Proposal

Inclusion of imatinib on the complementary list of the EML for the new indication of treatment of adults with Philadelphia chromosome positive (Ph+)/ BCR-ABL-positive acute lymphoblastic leukaemia.

Applicant

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WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical unit considered that there is sufficient evidence to justify the inclusion of imatinib on the EML for the treatment of Ph+ acute lymphoblastic leukaemia given its clinical impact and the feasibility of its appropriate use, noting its increasing availability for other cancer-related indications. Imatinib treatment for Ph+ acute lymphoblastic leukaemia is known to reduce mortality, improve quality of life and it has a favourable safety profile. Data for other tyrosine kinase inhibitors (e.g. dasatinib, ponatinib) are less mature.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Solid oral dosage form: 100 mg, 400 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Imatinib was added to the EML in 2015 for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumour (*1*). It was added to the EMLc for the same indications in 2019 (*2*). Imatinib has not previously been considered for inclusion on the EML or EMLc for the treatment of Ph+ acute lymphoblastic leukaemia.

Public health relevance (burden of disease)

Acute lymphoblastic leukaemia accounts for about 15% of all leukaemias (*3*). While it is the most common cancer in children, it is a relatively infrequent disease in adults. Excluding the paediatric population, its incidence increases with age and most new cases are diagnosed in individuals older than 65 years (*4*). Before the introduction of targeted therapies, the prognosis was particularly poor, with a 5-year survival of around 10–20% (*5*–*7*).

The Philadelphia chromosome is the most frequent cytogenetic abnormality in adults with acute lymphoblastic leukaemia. It is seen in about 30–40% of all cases (*8*). It corresponds to a translocation between the ABL-1 oncogene on chromosome 9 and a breakpoint cluster region (BCR) on chromosome 22, resulting in a fusion gene, BCR-ABL, that encodes a constitutively active tyrosine kinase (*9*). Before the introduction of tyrosine kinase inhibitors, the presence of the Philadelphia chromosome was associated with a significantly lower probability of remission and survival at 5 years (*10*).

Summary of evidence: benefits (from the application)

The applicants performed a literature search for randomized trials and systematic reviews of tyrosine kinase inhibitors in Ph+ acute lymphoblastic leukaemia, and conducted a meta-analysis of the results. Two systematic reviews (*11*, *12*) (used to identify relevant studies) and two small randomized trials (*13*, *14*) involving imatinib were identified. No data for other tyrosine kinase inhibitors were included in the application.

Randomized controlled trials

A small randomized trial in 32 centres in Germany between 2002 and 2005 randomly assigned 55 elderly participants (median age 68 years) with Ph+ acute lymphoblastic leukaemia to induction therapy with either imatinib (n = 28) or age-adapted chemotherapy (n = 27) (*13*). However, both groups later received imatinib during the consolidation chemotherapy, making it impossible to assess the effect of imatinib treatment on clinical outcomes.

Another German multicentre randomized trial conducted between 2004 and 2010 assessed the use of imatinib in Ph+ acute lymphoblastic leukaemia or lymphoid blast crisis of chronic myeloid leukaemia after allogeneic haematopoietic stem-cell transplantation (*14*). The trial included 57 participants who were randomized to either prophylactic imatinib after haematopoietic stem-cell transplantation (n = 26) or imatinib treatment based on detection of minimal residual disease (n = 29), again making it difficult to assess the effect of imatinib treatment.

Meta-analysis of cohort studies

The applicants performed a meta-analysis of eight comparative cohort studies identified from two published systematic reviews (*15–22*). All studies included individuals with Ph+ acute lymphoblastic leukaemia, and assessed the survival of individuals who received imatinib in addition to chemotherapy versus those who received chemotherapy alone. Typically, a proportion of participants also received an allogenic stem-cell transplantation with imatinib being used before and/or after the transplantation. Two of the studies evaluated a concurrent group (*15–17*) while six used data from historical patients (*18–22*).

The meta-analysis suggested that the use imatinib may significantly reduce mortality (risk ratio (RR) 0.50, 95% confidence interval (CI) 0.38 to 0.66); with 38 fewer deaths per 100 patients treated with imatinib. Four studies reported the median survival with and without imatinib (*15*, *18–20*). From these data, it was estimated that imatinib may increase overall survival by a median of 12 months compared with chemotherapy. Despite the large effect observed, there were concerns about: the risk of bias as most studies compared imatinib with historical data; and inconsistency, given that the magnitude of effect varied, with a proportion of studies showing a modest effect. Weighting these factors, the certainty of the evidence was therefore judged as low.

Summary of evidence: harms (from the application)

Cardiac toxicity, notably congestive heart failure, is a well known, albeit rare, adverse effect of treatment with tyrosine kinase inhibitors.

Data on potential toxicity of tyrosine kinase inhibitors when used for the treatment of Ph+ acute lymphoblastic leukaemia were limited. Only two of the studies included in the meta-analysis for the application reported adverse events (*15*, *16*). Meta-analysis of data from these studies indicated that the use of imatinib might increase the risk of adverse events, mainly due to cardiac toxicity (RR 1.31, 95% CI 0.73 to 2.36). In absolute terms, this would translate in eight more adverse events per 100 patients treated. The certainty of the evidence was judged as very low.

Additional evidence (not in the application)

In a separate application to the meeting of the Expert Committee, imatinib was also proposed for inclusion on the EMLc for treatment of acute lymphoblastic leukaemia in children, for which it is considered standard of care. Imatinib is included in the ALLTogether trial regimen for children and young adults with acute lymphoblastic leukaemia (*23*) and the EsPhALL trial regimen for children with Ph+ acute lymphoblastic leukaemia (*24*).

Several other trials studies have shown relevant benefits of imatinib in the paediatric population, with about 20% more participants alive at 5 years compared with before the introduction of imatinib for children with Ph+ acute lymphoblastic leukaemia (*25–28*).

WHO guidelines

WHO guidelines for the treatment of acute lymphoblastic leukaemia are not availble.

Clinical practice guidelines from the European Society of Medical Oncology recommend that all adults with Ph+ acute lymphoblastic leukaemia receive first-line treatment with imatinib or a second-generation tyrosine kinase inhibitor, in combination with chemotherapy (*12*). The National Comprehensive Cancer Network Guidelines also recommend treatment with a tyrosine kinase inhibitor in combination with multiagent chemotherapy or corticosteroids as induction treatment for Ph+ acute lymphoblastic leukaemia in adults, young adults and adolescents (*29*).

Costs/cost–effectiveness

Evidence on the cost–effectiveness of tyrosine kinase inhibitors in adults with acute lymphoblastic leukaemia is limited and does not include first-generation agents such as imatinib, which are generally more available and affordable. However, even second-generation tyrosine kinase inhibitors seem to be cost-effective (*30*).

Importantly, the patent of imatinib expired in 2016. However, this has not led to the expected rapid introduction of generic alternatives (*31*) nor to a

substantial price reduction: generic imatinib was introduced to the market only 8% below the price of the original and even today remains a costly medicine (*32*).

Availability

Imatinib has marketing approval from multiple national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. It is available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group supported the inclusion of imatinib on both the EML and EMLc for the treatment of adults and children with Ph+ acute lymphoblastic leukaemia based on evidence of relevant improvement in survival and acceptable safety. Despite also being associated relevant survival benefit, the available data for other tyrosine kinase inhibitors (dasatinib, ponatinib) are less mature. There is little evidence supporting their use in children and their global availability (including generics) is more limited. Therefore, the Working Group did not support the inclusion of tyrosine kinase inhibitors as a therapeutic class at this time.

Committee recommendations

The Expert Committee noted that Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia is the most frequent genetic subtype of acute lymphoblastic leukaemia in adults and historically has been associated with poor outcomes. The Committee acknowledged that the 5-year survival of adult patients with Ph+ acute lymphoblastic leukaemia with conventional chemotherapy was 10–20%, with a median survival of about 16 months. The addition of imatinib to conventional chemotherapy has halved the risk of premature death to around 50% and is now considered the standard of care for first-line treatment of Ph+ acute lymphoblastic leukaemia.

The Committee considered the results of the meta-analysis of comparative cohort studies included in the application, which indicated a difference in median survival of 12 months with the addition of imatinib to standard chemotherapy in the treatment of acute lymphoblastic leukaemia, based on low-quality evidence. The Committee considered this to represent a highly relevant improvement in clinical benefit. The Committee considered that the safety profile of imatinib is well known and generally acceptable, and that imatinib is already listed in the EML for chronic myeloid leukaemia and gastrointestinal stromal tumour.

The Committee took into account that accurate identification of the presence of the predictive biomarker (Ph+ or BCR/ABL fusion gene) requires

complex tests and is central to the appropriate use of any tyrosine kinase inhibitor in acute lymphoblastic leukaemia.

The Expert Committee therefore recommended the inclusion of imatinib on the EML for the treatment of adults with Ph+ acute lymphoblastic leukaemia, considering the overall survival benefit, acceptable safety profile, and that imatinib is off-patent and generic brands are becoming widely available. Noting the benefits of imatinib for paediatric patients with Ph+ acute lymphoblastic leukaemia, the Committee also extended the recommendation to inclusion on the EMLc. The Committee considered that other tyrosine kinase inhibitors (e.g. dasatinib, ponatinib) might have also have a place in the treatment of Ph+ acute lymphoblastic leukaemia but that currently, data were less mature. The Committee therefore did not support the inclusion of other tyrosine kinase inhibitors within the therapeutic class at this time but would welcome a future application when mature data are available.

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Osimertinib – addition – EML

Osimertinib — ATC Code: L01EB04

Proposal

Addition of osimertinib to the complementary list of the EML for first-line treatment of epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small-cell lung cancer.

Applicant

European Society for Medical Oncology (ESMO)

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department acknowledged that evidence suggests that osimertinib offers clinical value when compared with the first-generation tyrosine kinase inhibitors gefitinib and erlotinib in terms of overall survival gain and a more favourable toxicity profile. However, the technical department noted concerns about the accessibility of first-generation tyrosine kinase inhibitors already included on the 21st WHO EML. Furthermore, first-generation tyrosine kinase inhibitors (for which generics products are available) may also be more cost-effective and have less effect on health system budgets due to their lower price. The technical department concluded that these factors may argue against consideration of osimertinib for inclusion on the EML at this time. Finally, the technical department advised that future evaluation of osimertinib should take into account evolving data and the broader context of accessibility and prioritization.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Tablet: 40 mg, 80 mg (as mesylate)

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor. It has not been previously considered for inclusion on the EML.

In 2019, the Expert Committee recommended the addition of the first-generation EGFR tyrosine kinase inhibitor erlotinib to the EML for the treatment of EGFR mutation-positive non-small-cell lung cancer. Listing was recommended with a square box specifying gefitinib and the second-generation tyrosine kinase inhibitor afatinib as therapeutic alternatives. The Committee noted that these medicines were associated with relevant survival benefits for patients, acceptable toxicity and improvements in quality of life compared with chemotherapy. The Committee also noted the availability of generics and quality-assured diagnostic molecular tests for EGFR mutations (*1*).

Epidermal growth factor receptor is a transmembrane protein with kinase implicated in cell division, angiogenesis and apoptosis. Mutations in the EGFR gene (so-called driver mutations), of which many types exist but most concern deletions in exon 19 or substitutions of leucine for arginine (L858R) in exon 21, can contribute to uncontrolled cell proliferation. EGFR mutations (without prior exposure to tyrosine kinase inhibitors) are observed in about one in three patients with non-small-cell lung cancer (see the following section on public health relevance). First- and second-generation tyrosine kinase inhibitors are often associated with a pronounced initial response in patients with driver mutations but acquisition of secondary resistance to tyrosine kinase inhibitors and disease progression after several months of treatment are frequently observed. This acquired resistance is most frequently due to a mutation that substitutes methionine for threonine at amino acid position 790 (T790M). Osimertinib retains inhibitory activity in the presence of the T790M mutation.

Public health relevance (burden of disease)

Lung cancer is the leading cause of cancer death worldwide, with an estimated 1.7 million related deaths in 2018 (*2*). Lung cancer is a highly lethal malignancy, with an economic impact estimated at around US$ 8 billion in lost productivity in the BRICS countries (Brazil, Russia, India, China, and South Africa). Moreover, in the absence of wide coverage of an effective screening programme in place globally, lung cancer diagnoses occur in advanced stages in more than 60% of cases, with large regional variation (*3–5*).

Over 80% of lung cancers are classified as non-small-cell lung cancer (*6*). Targeted therapies have redefined treatment for patients with genomic alterations in driver oncogenes (e.g. EGFR mutations, anaplastic lymphoma

kinase rearrangements, ROS1 rearrangements, BRAF mutations, human epidermal growth factor receptor 2 (HER2) mutations or amplifications and neurotrophic tyrosine kinase (NTRK) 1–3 fusions) to guide the selection of treatments. However, these therapies are ineffective in most patients with non-small-cell lung cancer who have tumours that lack such genetic alterations. Gene-targeted therapies are now estimated to benefit less than 10% of patients with non-small-cell lung cancer, but this proportion might increase rapidly over time (*7*).

A meta-analysis and systematic reviews found an overall prevalence of EGFR mutation of about 30%, although this varies by world region, risk factors and population phenotype. For instance, the Asian–Pacific region has the highest prevalence of EGFR mutation (47%), followed by South America (36%), North America (22%), Africa (21%), Europe (15%) and Oceania (12%) (*8*–*10*).

Summary of evidence: benefits (from the application)

The phase III FLAURA trial was a double-blind, prospective clinical trial that compared osimertinib with standard first-generation tyrosine kinase inhibitors (gefitinib and erlotinib) for first-line treatment of EGFR-mutated locally advanced or metastatic non-small-cell lung cancer (*11*, *12*). The study randomized 556 participants in a 1:1 ratio to receive osimertinib 80 mg once daily, or standard treatment (gefitinib 250 mg once daily or erlotinib 150 mg once daily) until disease progression, unacceptable toxicity or consent withdrawal. At the time of primary analysis (data cut-off 12 June 2017) for the primary endpoint of progression-free survival, osimertinib was associated with a statistically significant improvement compared with standard treatment (median progression-free survival 18.9 months versus 10.2 months; hazard ratio (HR) for disease progression or death 0.46, 95% confidence interval (CI) 0.37 to 0.57). Osimertinib also demonstrated a significant progression-free survival benefit for participants with central nervous system metastasis, a common site of progression of non-small-cell lung cancer and frequently responsible for deterioration in quality of life (median progression-free survival 15.2 months versus 9.6 months; HR for disease progression or death 0.47, 95% CI 0.30 to 0.74) (*11*).

A final analysis (data cut-off 25 June 2019) was performed for the secondary endpoint of overall survival with a median duration of follow-up for overall survival of 35.8 months in the osimertinib group and 27.0 months in the comparator group (*12*). Median overall survival favoured the osimertinib group over the standard treatment group (median overall survival 38.6 months versus 31.8 months (HR 0.80, 95% CI 0.64 to 1.00), a 6.8-month survival gain in absolute terms (12). At 36 months, 54% of participants in the osimertinib group were alive compared with 44% in the comparator group.

Summary of evidence: harms (from the application)

From the final analysis of the FLAURA trial (*12*), adverse events of grade 3 or higher were reported in 42% and 47% of participants in the osimertinib group and standard treatment group, respectively. The most commonly reported adverse events possibly related to osimertinib treatment (investigator assessed) were diarrhoea (50%), paronychia (30%), dry skin (31%), stomatitis (25%) and dermatitis acneiform (25%). Serious adverse events were reported in 27% of the participants in each treatment arm. Decreased ejection fraction was reported in a greater proportion of participants in the osimertinib group than the standard treatment group (5% versus 2%). Similarly, QT prolongation was also reported in a greater proportion of participants in the osimertinib group than the standard treatment group (10% versus 4%). Compared with the primary analysis, there were no new reports of interstitial lung disease or pneumonitis, which were both reported in 2% and 1% of participants in the osimertinib and standard treatment groups, respectively (*11*, *12*).

In the osimertinib and standard treatment groups, dose interruptions occurred in 43% and 41% of participants, dose reductions in 5% and 4% and permanent discontinuation of treatment due to adverse events in 15% and 18%, respectively (*12*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for treatment of non-small-cell lung cancer are not available.

Costs/cost–effectiveness

A cost–effectiveness analysis was conducted of osimertinib compared with first- and second-generation EGFR tyrosine kinase inhibitors for first-line treatment of advanced EGFR-mutated non-small-cell lung cancer using direct costs from United States and Brazilian payer perspectives and a 10-year time horizon based on results from the FLAURA trial (*13*). In the base case, for the United States, the incremental costs per quality-adjusted life year (QALY) for osimertinib compared with erlotinib, gefitinib and afatinib were more than US$ 200 000 for each comparison. For Brazil, the incremental costs per QALY for osimertinib compared with erlotinib, gefitinib and afatinib were more than US$ 160 000 for each comparison. Applying a cost–effectiveness threshold of three times the gross domestic product per capita for each country, the authors concluded that osimertinib was not a cost-effective intervention at current prices in either country.

In October 2020, the National Institute for Health and Care Excellence of the United Kingdom of Great Britain and Northern Ireland recommended coverage under the National Health System for osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer, after confidential commercial arrangements with the manufacturer were negotiated resulting in lower price and cost–effectiveness estimates within the acceptable range for use of National Health System resources (*14*).

Availability

Osimertinib (trade name Tagrisso, Astra Zeneca) has regulatory approval in 40 countries including the United States, Japan and in Europe for frontline treatment of EGFR-mutated non-small-cell lung cancer. It has primary patent protection until 2032.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of osimertinib on the EML at this time. The Working Group noted that earlier tyrosine kinase inhibitors currently listed on the EML for EGFR-mutated non-small-cell lung cancer are available as generics and are more likely to be affordable, accessible treatment options for patients and health systems. The Working Group noted that osimertinib has a demonstrated meaningful overall survival benefit compared with first-generation tyrosine kinase inhibitors and meets the criteria of the European Society for Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 score. However, the current price of osimertinib is prohibitively high for both patients and health systems, and it has not been found to be cost-effective at current prices in some analyses. The Working Group also noted the requirement for accompanying diagnostic testing, which has variable and limited availability in low- and middle-income settings.

Osimertinib treatment is only given to patients whose tumours exhibit EGFR-tyrosine kinase inhibitor sensitizing mutations detected by molecular tests validated by regulatory agencies. The need for molecular testing is also a requirement for osimertinib treatment according to existing treatment guidelines of medical oncology societies (*15*). The EGFR gene mutation test was added to the WHO Model List of Essential In-Vitro Diagnostics in 2020 (*16*).

The European Society for Medical Oncology clinical practice guidelines for metastatic non-small-cell lung cancer recommend osimertinib as the preferred option for first-line treatment of non-small-cell lung cancer patients with sensitizing EGFR mutations (ESMO-MCBS v1.1 score: 4) (*17*). Current National Comprehensive Cancer Network (NCCN) guidelines for NSCLC also recommend osimertinib as preferred first-line therapy for EGFR mutation positive NSCLC (category 1, high-level evidence) (*15*).

Committee recommendations

The Expert Committee acknowledged the treatment of lung cancer to be complex and recognized the need to provide the best available care within the context of both non-small-cell lung cancer and small-cell lung cancers. Over the past decade, the treatment outcomes for advanced non-small-cell lung cancer have improved with new treatment models involving targeted therapy based on the molecular and biological characteristics of the cancer. For EGFR mutation-positive non-small-cell lung cancer, the Committee recalled its recommendations in 2019 to include erlotinib, gefitinib and afatinib as therapeutic alternatives for this indication. These medicines are associated with improved quality of life and longer overall survival compared with cytotoxic chemotherapy in patients with the EGFR driver mutation.

The Expert Committee noted that the application to list osimertinib was based on the results of a single randomized control trial (FLAURA), in which osimertinib was compared to physician's choice of erlotinib or gefitinib. Interim trial results showed that osimertinib extended overall survival compared with the two first-generation EGFR tyrosine kinase inhibitors. However, the Committee considered that overall survival data, while promising, were still immature and therefore confidence that osimertinib prolongs survival compared with erlotinib and gefitinib is limited.

The Expert Committee also noted that the current price of osimertinib is very high, and several analyses have concluded it is not cost-effective. Meanwhile, first- and second-generation tyrosine kinase inhibitors, including those currently included on the EML, are available as generic products and are more likely to be affordable, accessible treatment options for patients and health systems. The Committee considered the option of including osimertinib as an additional therapeutic alternative to the EGFR tyrosine kinase inhibitors already included on the EML, thereby allowing selection of osimertinib at the country level. However, given the difference in current prices, the Committee decided against this option due to the risk of considerable additional expenditure at the country level.

Therefore, the Expert Committee did not recommend the inclusion of osimertinib on the EML at this time. However, the Committee considered that the current evidence for osimertinib was promising and requested that an application with updated survival data be submitted for consideration at the next Expert Committee meeting.

Without committing a future Expert Committee to a favourable recommendation to include osimertinib on the EML, the Committee recommended that osimertinib be flagged to the Medicines Patent Pool as a candidate for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of

negotiations might provide important insight for future EML consideration on potential accessibility of this medicine in low- and middle-income countries.

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Pertuzumab – addition – EML

Pertuzumab — ATC Code: L01FD02

Proposal

Addition of pertuzumab to the complementary list of the EML for use in combination with trastuzumab and chemotherapy for first-line treatment of adults with human epidermal growth factor receptor 2 (HER2)-positive locally recurrent unresectable or metastatic breast cancer.

Applicant

F. Hoffmann-La Roche Ltd, Basel, Switzerland

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department noted that there was evidence of clinical benefit for pertuzumab. The feasibility of the inclusion of pertuzumab in national EMLs, particularly for low- and middle-income countries, is uncertain, when access to trastuzumab remains limited because of costs and diagnostic capacity. The addition of pertuzumab, in light of the increased focus on and availability of trastuzumab biosimilars, has an opportunity cost that may further limit inclusion of HER2-positive targeted therapies in national EMLs and benefit packages as part of universal health coverage. The duration of therapy with pertuzumab is uncertain, which may also affect its accessibility in low- and middle-income countries. Given these considerations, increasing access to trastuzumab, including through WHO prequalification, should be considered a priority before reconsidering the inclusion of pertuzumab on the EML.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Concentrate solution for infusion: 420 mg/14 mL in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The Expert Committee considered an application for the inclusion of pertuzumab on the EML for the treatment of early-stage and metastatic HER2-positive breast cancer in 2019, but did not recommended its listing. The Committee considered that the available evidence did not demonstrate a clinically meaningful survival benefit in early stage disease, and that there was important uncertainty about the estimated magnitude of survival benefit in metastatic disease, with results seen in the CLEOPATRA trial not replicated in other trials (*1*).

The Committee acknowledged that pertuzumab was associated with a relevant survival benefit, well beyond the established threshold, as first-line treatment of metastatic breast cancer, based on the results reported in the CLEOPATRA trial. However, the Committee expressed reservations about the generalizability of the results from CLEOPATRA in metastatic breast cancer and consistency of the clinical effectiveness of pertuzumab in studies in both early and metastatic breast cancer.

The Committee noted that only about 10% of patients in CLEOPATRA trial had received trastuzumab in the adjuvant or neoadjuvant setting. The Committee was concerned that the observed survival gains may not therefore be generalizable to patients with metastatic disease who have received prior adjuvant or neoadjuvant trastuzumab, making the magnitude of benefit in this population subgroup uncertain. The Committee also noted the results reported in the MARIANNE trial, where pertuzumab in combination with trastuzumab emtansine (T-DM1) was not shown to have greater clinical benefit than trastuzumab plus chemotherapy or T-DM1 alone. The Committee was unable to reconcile the differences in outcomes reported in the MARIANNE and CLEOPATRA trials.

The Committee also noted that the relevant survival gains observed in the CLEOPATRA trial for metastatic breast cancer were not replicated in trials of pertuzumab in early stage breast cancer. The Committee accepted that trial results suggest pertuzumab offers a small incremental overall and disease-free survival benefit compared with placebo, based on an analysis at around 3 years median follow-up. The Committee considered that continued follow-up was important to assess long-term overall survival, but thought it unlikely that the magnitude of benefit would be greater with longer follow-up, given that anti-HER2 treatments are typically associated with a reduction in early recurrences, followed by a plateau effect.

In the current resubmission, the applicant has consolidated the most recent datasets and published additional scientific information that shows positive results supporting the pertuzumab–trastuzumab combination as the

standard of care in first-line treatment of HER2-positive metastatic breast cancer. To complement these data, the application includes supplementary evidence to demonstrate survival benefits in the real-world setting.

Public health relevance (burden of disease)

Breast cancer is the leading cause of cancer death in women globally, responsible for 6.6% of all cancer deaths in 2018 (*2*). High incidence and low mortality rates are seen in high-income countries, with low incidence and high mortality rates recorded in low- and middle-income countries. The overall 5-year survival rates for high-income countries are estimated to be higher than 85%. In comparison, in low- and middle-income countries, 5-year survival rates are reported to range between 38% and 60% (*3*).

While improved early detection and advances in systemic therapy for the early-stage disease have resulted in some decline in breast cancer mortality since 1989, metastatic breast cancer remains largely incurable with a median survival of about 24 months (*4*). Factors associated with poor survival include age ≥ 50 years, visceral disease, shorter disease-free interval, aneuploid tumours, tumours with a high S-phase fraction, p53 accumulation, low BCL2 gene expression, negative hormone receptor status, and positive HER2 status (*5*). Five-year survival for patients with metastatic disease is about 18% in Europe (*6*).

Many cytotoxic agents are available for the treatment of metastatic breast cancer that are used singly or in combination (anthracyclines, taxanes, alkylating agents and vinca alkaloids). Used as single agents, they produce response rates of 20–80%; however, complete responses are rare and short-lived, and disease progression is almost inevitable (*7*, *8*). HER2 is involved in regulating cell growth, survival and differentiation (*9*), thus the HER2 receptor has emerged as one of the most important targets for breast cancer treatment. Amplification and/or overexpression of HER2 occurs in about 18–22% of breast cancers (*10*, *11*). HER2-positivity is associated with increased tumour aggressiveness, higher rates of recurrence and increased mortality (*11–16*). The median age of patients presenting with HER2-positive breast cancer is the mid-50s, about 5 years younger than the general breast cancer population (*17*).

Summary of evidence: benefits (from the application)

The main sources of evidence for efficacy of pertuzumab in treatment of metastatic breast cancer presented in the application were from the CLEOPATRA, PUFFIN and PERUSE trials.

CLEOPATRA (18–21)

This was a multicentre, randomized, double-blind, placebo-controlled, phase III study in participants with HER2-positive metastatic or locally recurrent non-

resectable breast cancer who had not previously received anti-HER2 therapy or chemotherapy for metastatic disease. The primary efficacy endpoint was progression-free survival assessed by an independent review facility. Key secondary efficacy endpoints included overall survival and overall response rate assessed by an independent review facility. A total of 808 participants were randomized in a 1:1 ratio to pertuzumab + trastuzumab + docetaxel (n = 402) or placebo + trastuzumab + docetaxel (n = 406).

Results showed a statistically significant and clinically meaningful improvement in progression-free survival assessed by an independent review facility in the pertuzumab arm compared with the placebo arm (hazard ratio (HR) 0.62; 95% confidence interval (CI) 0.51 to 0.75; $P < 0.001$), with an increase of 6.1 months in median progression-free survival (12.4 months in the placebo arm versus 18.5 months in the pertuzumab arm). Analyses of progression-free survival by clinically relevant patient subgroups suggested that the benefit of pertuzumab in combination with trastuzumab and docetaxel was observed consistently in all prespecified subgroups tested, including those based on geographic region, prior treatment, age, race, presence of visceral disease, hormone receptor status, and HER2 immunohistochemistry or fluorescent in situ hybridization status.

The final analysis of overall survival from the CLEOPATRA trial (data cut-off 11 February 2014) found that the median overall survival estimates were 40.8 months with placebo + trastuzumab + docetaxel and 56.5 months with pertuzumab + trastuzumab + docetaxel (HR 0.68, 95% CI 0.56 to 0.84). At the time of data cut-off, 320/406 (78.8%) participants in the placebo + trastuzumab + docetaxel arm and 284/402 (70.6%) participants in the pertuzumab + trastuzumab + docetaxel arm had experienced a progression-free survival event, according to the investigator. The median progression-free survival duration of 12.4 months in the placebo arm and 18.7 months in the pertuzumab arm was consistent with the previous analyses.

An end-of-study analysis of the CLEOPATRA trial was conducted based on a clinical cut-off date of 23 November 2008 (*21*). Median overall survival estimates at the end of study (> 8 years of follow-up) were 40.8 months with placebo + trastuzumab + docetaxel and 57.1 months with pertuzumab + trastuzumab + docetaxel (HR 0.69, 95% CI 0.58 to 0.82; $P < 0.0001$). The 8-year landmark overall survival rates were 37% in the pertuzumab-treated group and 23% in the placebo-treated group.

PUFFIN (22)

This was a randomized, double-blind, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab+ docetaxel versus placebo + trastuzumab + docetaxel in 243 Chinese participants with

previously untreated HER2-positive metastatic breast cancer; it is a bridging study to CLEOPATRA. The primary endpoint was investigator-assessed progression-free survival; secondary endpoints included overall response rate (in participants with measurable baseline disease), overall survival and safety.

Compared with placebo + trastuzumab + docetaxel, treatment with pertuzumab + trastuzumab+ docetaxel resulted in a clinically meaningful improvement in investigator-assessed progression-free survival (stratified HR 0.69, 95% CI 0.49 to 0.99), corresponding to a 31% reduction in the risk of disease progression or death. The observed magnitude of treatment effect was not fully consistent with the CLEOPATRA data. Median progression-free survival was 12.4 months in the placebo + trastuzumab + docetaxel arm versus 14.5 months in the pertuzumab + trastuzumab+ docetaxel arm. Overall survival data were not considered mature at the time of the clinical cut-off date. The median time to death had not been reached in either treatment arm at the time of the cut-off.

PERUSE (23, 24)

This was a multicentre single-arm phase IIIb study to assess the safety and efficacy of physician's choice taxane with pertuzumab and trastuzumab as first-line therapy for HER2-positive locally recurrent or metastatic breast cancer.

Patients with inoperable HER2-positive advanced locally recurrent or metastatic breast cancer and no prior systemic therapy (except endocrine therapy) received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab and pertuzumab until disease progression or unacceptable toxicity. The primary endpoint was safety; secondary endpoints included overall response rate and progression-free survival. Participants received a median of 16.2 months of study treatment (4.2 months of taxane therapy and 16.1 months of anti-HER2 therapy). At the date of the clinical cut-off for the final analysis (26 August 2019), the median duration of follow-up was 68.7 months (95% CI 67.5 to 69.3 months), corresponding to 5.7 years. Survival results were consistent with the CLEOPATRA trial: median progression-free survival 20.7 months (95% CI 18.9 to 23.1 months) in PERUSE versus 18.7 months in CLEOPATRA; median overall survival 65.3 months (95% CI 60.9 to 70.9 months) in PERUSE versus 57.1 months in CLEOPATRA. Maintenance endocrine therapy, which was allowed in PERUSE but not in CLEOPATRA, may explain the more favourable overall survival in participants with HER2-positive disease in PERUSE.

The application included an overview of additional supportive studies for pertuzumab in HER2-positive metastatic breast cancer (*25*–*33*), including a real-world study on the use of pertuzumab plus trastuzumab and taxane as first-line treatment of HER2-positive metastatic breast cancer (*34*).

Summary of evidence: harms (from the application)

Safety data from 19 clinical studies indicate that pertuzumab, combined with trastuzumab and a range of other therapeutic agents, has an acceptable safety profile. No new or unexpected safety findings were encountered other than those side-effects known for agents that target the HER family of receptors; these include diarrhoea, fatigue and nausea as the most frequently reported adverse events with single-agent pertuzumab. The incidence of haematological toxicities such as leukopenia and febrile neutropenia is low. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction, has been reported. In the CLEOPATRA study, the rates of symptomatic and asymptomatic left ventricular systolic dysfunction were not higher in participants receiving pertuzumab + trastuzumab + docetaxel than in those receiving placebo + trastuzumab + docetaxel (*18*). However, participants who have received prior anthracyclines or radiotherapy to the chest area may be at higher risk of decreased left ventricular ejection fraction.

The safety of pertuzumab has been evaluated in more than 6000 participants in phase I–III trials in both early and metastatic breast cancer settings including CLEOPATRA (n = 808), NEOSPHERE (n = 417), TRYPHAENA (n = 225) and APHINITY (n = 4804). The safety of pertuzumab was generally consistent across the studies. However, the incidence and most common adverse drug reactions varied depending on whether pertuzumab was administered as monotherapy or in combination with other antineoplastic agents.

Pooled safety data from these studies indicate that the most common adverse events (all grades) with pertuzumab occurring in at least 30% of patients were diarrhoea (67.9%), alopecia (63.1%), nausea (60.8%), fatigue (44.3%), neutropenia (31.4%) and vomiting (30.0%). The most common grade 3 and 4 adverse events occurring in at least 10% of patients were neutropenia (24.2%) and febrile neutropenia (11.8%).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for treatment of metastatic HER2-positive breast cancer are not available.

The combination regimen of pertuzumab, trastuzumab plus taxane chemotherapy is recommended for first-line treatment of HER2-positive metastatic breast cancer in several international guidelines (*35–38*).

Costs/cost–effectiveness

In the United States, the wholesale acquisition cost of one vial of pertuzumab 420 mg is US$ 5292 per vial and US$ 100 548 per episode of care (18 cycles). In France, Germany, Italy, Spain and the United Kingdom of Great Britain and Northern Ireland, ex-factory list prices for pertuzumab range from € 2221 to € 3037 per vial, or € 42 199 to € 57 703 per episode of care.

In low- and lower-middle-income countries, the manufacturer (Roche) has developed an international differential pricing model which aligns innovative medicine prices (including pertuzumab) to a purchasing parity-adapted formula, factoring in gross domestic product per capita, public health care investment and the United Nations Human Development Index to ensure that the prices are as fair as possible. This model was applied in several low- and middle-income countries together with patient assistance programmes. However, information about the effect of this model on accessibility and affordability is limited. Reimbursement agreements involving special pricing were reached with governments in Brazil, Lebanon, Morocco and Uruguay.

Special price agreements have also been negotiated and resulted in positive reimbursement decisions for the combination of pertuzumab plus trastuzumab for metastatic HER2-positive breast cancer in several high-income countries including France, Germany, Ireland, Spain and the United Kingdom.

Availability

As of June 2020, pertuzumab has been approved in more than 117 countries worldwide for treatment of metastatic breast cancer.

Other considerations

MARIANNE (39)

In consideration of the application for pertuzumab in 2019, the Expert Committee noted the overall survival results from the MARIANNE trial, a randomized multicentre phase III study designed to evaluate TDM-1 alone or in combination with pertuzumab compared with trastuzumab plus taxane chemotherapy as first-line treatment of HER2-positive metastatic breast cancer. A total of 1095 participants were randomized 1:1:1 to the three treatment arms. In particular, the Committee noted that overall survival was similar in all three treatment arms, with all regimens resulting in median overall survival longer than 50 months. For the trastuzumab plus taxane arm, median overall survival was 50.9 months (*1*). In contrast, in the CLEOPATRA trial, the median overall survival was 40.8 months in the trastuzumab plus docetaxel arm, and 57.1 months in the pertuzumab plus trastuzumab plus docetaxel arm.

To clarify concerns raised by the Expert Committee in 2019, the current application included information about the MARIANNE trial, including rationale, study design, efficacy results for progression-free survival (the primary endpoint) and safety. It concluded that it was not appropriate to draw comparisons between the CLEOPATRA and MARIANNE studies due to differences in study design, objectives and patient populations.

Comments from the EML Cancer Medicines Working Group

The Working Group acknowledged that the updated data from the CLEOPATRA trial and additional evidence presented from PERUSE and PUFFIN trials, demonstrated relevant benefit in overall survival of pertuzumab (in combination with trastuzumab) in treatment of metastatic breast cancer. The Working Group considered that the inclusion of pertuzumab on the EML for treatment of metastatic HER2-positive breast cancer, in combination with trastuzumab and a taxane, could be supported from a clinical perspective.

However, the Working Group acknowledged that the use of combination therapy with trastuzumab and pertuzumab, both high-priced medicines, would be a financial challenge for patients and health systems, and access in many settings would be limited. The Working Group also noted that affordability of and access to trastuzumab (included on the EML model list since 2015) remains very limited in many resource-constrained settings, and the addition of another high-priced biological medicine would likely compound this problem. Increasing the availability of biosimilars will be critical to improving affordability and access. The Working Group therefore concluded that financial considerations precluded its support for inclusion of pertuzumab on the EML.

In addition, the Working Group highlighted that future consideration should be given to the optimal duration of pertuzumab treatment for patients with metastatic breast cancer. Clinical data on this question are currently lacking and should be supported as a research priority by research funding agencies.

Committee recommendations

The Expert Committee noted the meaningful clinical benefit of pertuzumab in metastatic HER2-positive breast cancer when used in combination with trastuzumab and a taxane (e.g. docetaxel). Based on the results of the CLEOPATRA trial, the addition of pertuzumab to trastuzumab and docetaxel for first-line treatment of metastatic breast cancer increased overall survival by about 16 months.

The Committee noted the high price of the combination therapy with trastuzumab and pertuzumab, which would present significant financial challenges to patients and health systems, and limit access in many settings. The Committee also considered the requirement of diagnostic molecular tests for

determining HER2 status (immunohistochemistry and in-situ hybridization) conducted in highly specialized laboratories and requiring skilled technicians, which may not be widely available and affordable in many low- and middle-income settings. The limited availability of adequate diagnostic infrastructure is a substantial barrier to the appropriate use of HER2 inhibitors and other targeted therapies that should be addressed.

The Committee also acknowledged the recommendation against listing of pertuzumab made by the Cancer Working Group based on the concerns outlined in the previous section. The Committee also supported the suggestion of the Cancer Working Group of the need to generate clinical data on the optimal duration of pertuzumab treatment, as shorter treatment duration may make this medicine more affordable. Studies examining this question should be supported as a research priority.

The Expert Committee did not recommend the listing of pertuzumab on the EML for the treatment of metastatic HER2-positive breast cancer. Despite the relevant benefit in overall survival when adding pertuzumab to trastuzumab and a taxane shown in the CLEOPATRA trial, the use of combination therapy with trastuzumab + pertuzumab, both high-priced medicines, would be a significant financial challenge for patients and health systems. Indeed, despite trastuzumab being on the EML since 2015 and the availability of biosimilars, access to and affordability of trastuzumab remains very limited in resource-constrained settings.

The increasing number of trastuzumab biosimilars, including those that have been prequalified by WHO, might help increase access. The Committee decided, however, that also adding pertuzumab to the EML at this point could well result in considerable additional expenditure at the country level, using resources that should first be allocated to improving trastuzumab access. The expectation of the Committee is that, in the near future, there will be pertuzumab biosimilars that can be rapidly approved, with the aim of promoting competition among alternatives and allowing for the selection of optimal cheaper combinations of trastuzumab and pertuzumab produced by different companies.

The Committee also recommended that WHO continue to work on existing approaches to managing prices and evaluate alternative strategies to improve affordability and access in order to reduce the global burden of cancer.

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Zanubrutinib – addition for chronic lymphocytic leukaemia/small lymphocytic lymphoma – EML

Zanubrutinib **ATC Code: L01EL03**

Proposal

Addition of zanubrutinib to the complementary list of the EML for the treatment of relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma in adult patients who have received at least one prior therapy.

Applicant

BeiGene Co., Ltd, Beijing, China

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that at the current time there was insufficient evidence to support inclusion of zanubrutinib on the EML because of the lack of mature data substantiating a significant clinical effect and concerns about the toxicity profile (particularly the incidence of severe infections).

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Capsule: 80 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Zanubrutinib has not previously been considered for inclusion on the EML.

Medicines currently included on the EML for chronic lymphocytic leukaemia are bendamustine, chlorambucil, cyclophosphamide, fludarabine, prednisolone and rituximab, recommended for inclusion as part of the

comprehensive review of cancer medicines undertaken by the Expert Committee in 2015 (*1*).

Zanubrutinib belongs to the class of Bruton tyrosine kinase inhibitors which are currently not listed on the EML for any indication. Continuous activation of Bruton tyrosine kinase plays an important role in the proliferation of malignant B-cells, which can be counteracted by Bruton tyrosine kinase inhibitors.

Public health relevance (burden of disease)

Chronic lymphocytic leukaemia/small lymphocytic lymphoma is the main non-Hodgkin lymphoma subtype, occurring mainly in middle-aged and elderly people. Chronic lymphocytic leukaemia and small lymphocytic lymphoma are indolent (slow-growing) B-cell malignancies that are often considered different clinical presentations of same disease. The main difference is whether a patient presents with an elevated lymphocyte count (chronic lymphocytic leukaemia) or with adenopathy alone (small lymphocytic lymphoma). Although mostly considered an indolent disease, chronic lymphocytic leukaemia/small lymphocytic lymphoma has a wide spectrum of clinical presentation and it remains a life-limiting illness.

In many high-income countries, chronic lymphocytic leukaemia is the most common leukaemia in adults and accounts for 5–11% of non-Hodgkin lymphomas (*2*). The annual incidence is reported as 4.2 per 100 000 people, increasing to over 30.0 per 100 000 in those aged 80 years and older (*3*). Chronic lymphocytic leukaemia is less prevalent in Asian countries where it accounts for 1–3% of non-Hodgkin lymphomas and has an age-adjusted incidence rate of 0.2–0.3 per 100 000 (*2*,*4*). Relative survival is correlated with age. The 5-year relative survival of chronic lymphocytic leukaemia/small lymphocytic lymphoma patients in the United States aged 0–19 years, 20–64 years and > 65 years has been reported as 93%, 92% and 81%, respectively (*5*).

The treatment options for chronic lymphocytic leukaemia have changed since the introduction of inhibitors of the B-cell receptor signalling pathway (*6*). According to the latest guidelines from the United States National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology, ibrutinib is the preferred choice for patients with relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma, regardless of patient's age and comorbidities (*7*,*8*). Allogeneic hematopoietic stem cell transplantation may be considered in patients with relapsed chronic lymphocytic leukaemia/small lymphocytic lymphoma with TP53 mutations or 17p deletion, or in patients whose disease is refractory to inhibitor therapy (*7*).

Globally, the absolute number of deaths due to chronic lymphocytic leukaemia increased by 70% from 1990 to 2017. Of note, age-adjusted death rates

have decreased in high-income regions, largely due to access to and availability of effective treatments, but have increased in many lower-income settings where effective treatment is not available or affordable (*9*).

Summary of evidence: benefits (from the application)

The application presented the results of study BGB-3111-205, a single-arm, open-label, multicentre phase II trial that evaluated the efficacy and safety of zanubrutinib 160 mg twice daily in 91 participants with relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma (*10*). The primary endpoint was overall response rate assessed by an independent review committee; secondary endpoints included duration of response, time to response, progression-free survival and safety. After a median follow-up of 15.1 months, 77 participants (85%) achieved an objective response. Three participants (3%) achieved a complete response, 54 (59%) achieved a partial response and 20 (22%) achieved a partial response with lymphocytosis. After a median follow-up of 12.9 months for progression-free survival, 87% of participants had neither progressed nor died at 12 months; the median progression-free survival was not reached.

The application also presented a summary of results from phase I pharmacokinetic and dose-finding studies of zanubrutinib (*11*, *12*). Of 56 participants with relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma in the phase I GBG-3111-AU-003 study, 53 (95%) achieved an objective response (one with complete response, 45 with partial response and seven with partial response with lymphocytosis) (*11*). Median progression-free survival has not been reached and 12-month estimated progression-free survival was 100%.

Direct comparative data of zanubrutinib with other Bruton tyrosine kinase inhibitors for chronic lymphocytic leukaemia/small lymphocytic lymphoma are lacking. The application presented indirect comparisons of efficacy reported for zanubrutinib (*10*) and the first-generation Bruton tyrosine kinase inhibitor, ibrutinib (*13–15*). Objective response rates (assessed by an independent review committee) were 85% for zanubrutinib and 63% for ibrutinib. Reported progression-free survival rates at 6 months were about 92% for zanubrutinib and 86–88% for ibrutinib. Progression-free survival rates at 12 months were 87% for zanubrutinib and 61–67% for ibrutinib.

Summary of evidence: harms (from the application)

Safety results from phase I and II trials of zanubrutinib were presented (*10–12*).

In study BGB-3111-205, all participants reported at least one adverse event. Fifty-eight (64%) participants reported at least one grade 3 adverse event. Grade 4 and 5 adverse events were reported in eight (9%) and three

(3%) participants, respectively. The most frequently reported adverse events of any grade were neutropenia (69%), upper respiratory tract infection (45%), thrombocytopenia (42%), petechiae/purpura/contusion (35%), anaemia and haematuria (each 30%), hypokalaemia (25%), cough (24%) and increased carbon dioxide and hyperglycaemia (each 21%). The most common grade 3 adverse events were neutropenia (37%), thrombocytopenia (14%), lung infection/pneumonia (12%), upper respiratory tract infection (10%), and anaemia (9%). One third of participants reported at least one serious adverse event, the most common being lung infection (in seven participants), pneumonia (in three), upper respiratory infection (in three) and bronchitis (in two). Three participants experienced fatal grade 5 adverse events. Eight participants discontinued treatment with zanubrutinib due to adverse events and seven participants required at least one dose reduction (*10*).

From an indirect comparison with ibrutinib for the treatment of relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma, zanubrutinib was associated with lower rates of severe bleeding (2% versus 3%), atrial fibrillation (0% versus 6%) and treatment discontinuation due to adverse events (9% versus 12%) (*10*, *13*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for treatment of relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma are not available.

Zanubrutinib has been recommended for treatment of relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma in recent guidelines of the Chinese Society of Clinical Oncology, regardless of the presence of del (17p)/TP53 mutation (*8*).

Costs/cost–effectiveness

No cost–effectiveness analysis data for zanubrutinib were presented in the application.

The price for zanubrutinib in the United States is US$ 12 935 per bottle (120 capsules), corresponding to 30 days of treatment at the recommended dose. The price for zanubrutinib in China is ¥ 11 300 per bottle (64 capsules). The monthly treatment cost is ¥ 22 600. Comparatively, the first-generation Bruton tyrosine kinase inhibitor, ibrutinib, is listed in China priced at ¥ 22 680 per month for patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma.

Availability

Zanubrutinib has regulatory approval from the National Medical Products Administration of the People's Republic of China for the treatment of patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma who have received at least one prior therapy.

Regulatory submissions have also been made in Australia, Canada, Europe and Israel.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of zanubrutinib on the EML for treatment of relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and short follow-up), important toxicity concerns, high price and unknown cost–effectiveness.

Committee recommendations

The Expert Committee noted that targeted therapy with Bruton tyrosine kinase inhibitors is now emerging as the cornerstone of chronic lymphocytic leukaemia treatment in high-income countries, replacing chemoimmunotherapy as the accepted standard of care because it is more effective, has less acute toxicity and minimal risk of development of secondary leukaemias.

The Committee considered that the application for inclusion of zanubrutinib on the EML for treatment of relapsed/refractory chronic lymphocytic leukaemia was premature. The available data on efficacy and safety were limited to one phase II single-arm trial, with a small number of participants. Comparative evidence of efficacy and safety versus other treatments, for example ibrutinib, was also lacking. The available data were therefore considered insufficient to evaluate the clinical benefit and safety of zanubrutinib as an essential medicine at this time.

The Committee also noted that zanubrutinib is expensive, has unknown cost–effectiveness, and has very limited global regulatory approval and availability. Therefore, the Committee did not recommend its inclusion on the EML for the treatment of relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma.

However, recognizing the emerging important role of Bruton tyrosine kinase inhibitors, as a therapeutic class in the treatment of chronic lymphocytic leukaemia in both the first- and second-line treatment settings, the Committee advised that it would welcome an application including zanubrutinib and other Bruton kinase inhibitors for consideration as therapeutic alternatives for inclusion on the EML in the future when mature data are available.

Without committing a future Expert Committee to a favourable recommendation to include zanubrutinib on the EML, the Committee recommended that zanubrutinib be flagged to the Medicines Patent Pool as a candidate for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this medicine in low- and middle-income countries.

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Zanubrutinib – addition for mantle cell lymphoma – EML

Zanubrutinib **ATC Code: L01EL03**

Proposal

Addition of zanubrutinib to the complementary list of the EML for the treatment of adult patients with relapsed/refractory mantle cell lymphoma who have received at least one prior therapy.

Applicant

BeiGene Co., Ltd, Beijing, China

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that at the current time, there was insufficient evidence to support inclusion of zanubrutinib in WHO EML because of the lack of mature data substantiating a significant clinical effect and concerns about the toxicity profile (particularly rates of severe infections).

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strength(s)

Capsule: 80 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Zanubrutinib has not previously been considered for inclusion on the EML.

The Model List does not currently include any medicines specifically for the treatment of mantle cell lymphoma.

Public health relevance (burden of disease)

Mantle cell lymphoma is an uncommon subtype of non-Hodgkin lymphoma, accounting for between 2% and 10% of all non-Hodgkin lymphomas (*1*). In 2018, the global incidence of non-Hodgkin lymphoma was 6.7 per 100 000 people (*2*). Mantle cell lymphoma has been reported to account for 7.8% of non-Hodgkin lymphoma in developed regions and 3.8% in developing regions (*3*). In Europe and the United States, average incidence rates for mantle cell lymphoma of about 0.5 cases per 100 000 person-years have been reported, with a male-to-female ratio of 2.3–5.0 to 1 and a median age at diagnosis of about 70 years (*4*).

Mantle cell lymphoma is an aggressive disease with a poor prognosis and poor survival. During 2010 to 2016, the 5-year relative survival of patients with mantle cell lymphoma in the United States was 61.9%, and the relative survival was significantly correlated with age. The 5-year relative survival of patients with mantle cell lymphoma aged 20–64 years and > 65 years was 71.2% and 54.9%, respectively (*5*).

Outcomes of treatment for mantle cell lymphoma vary widely. Patients can have an aggressive presentation and die from the disease in less than 6 months, or can have a slowly progressing clinical course with long survival of more than 10 years (*6*). More than 90% of patients present with advanced-stage disease (stage 3–4) (*7*).

For several decades, the gold standard of first-line treatment was chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone, which has been used more recently in combination with the anti-CD20 antibody rituximab. Younger patients have been treated with more aggressive chemoimmunotherapy, with high doses of cyclophosphamide as part of a hyper-CVAD regimen (cyclophosphamide, vincristine, doxorubicin and dexamethasone). High doses of cytarabine were also used in other regimens for clinically fit patients with mantle cell lymphoma younger than 65 years old. Maintenance treatment with rituximab was shown to prolong response duration after rituximab-containing chemotherapy (*8–11*). Although standard chemoimmunotherapy is associated with a high overall response rate, treatment is not curative, and most patients will experience relapse. The rate of complete response is less than 50%, with median overall survival of 3–4 years (*10*, *12*). Median survival after first relapse of mantle cell lymphoma is 1–2 years (*13*).

Allogenic haematopoietic stem cell transplantation may also be an option for the treatment of relapsed/refractory mantle cell lymphoma. However, many patients will not be candidates for such intensive treatment approaches due to advanced age and comorbid illness (*13*).

Summary of evidence: benefits (from the application)

The application presented the results of study BGB-3111-206, a single-arm, multicentre phase II trial that evaluated the efficacy and safety of zanubrutinib

160 mg twice daily in 86 participants with confirmed relapsed/refractory mantle cell lymphoma (*14*). The primary endpoint was overall response rate assessed by an independent review committee; secondary endpoints included duration of response, time to response, progression-free survival and safety. After median follow-up of 18.4 months, 72 participants (84%) achieved an objective response, with 59 participants (67%) achieving a complete response. After a median follow-up of 16.4 months from the initial response, the estimated median duration of response was 19.5 months. After a median follow-up of 19.2 months, the estimated median progression-free survival was 22.1 months with an estimated 76% of participants alive and without disease progression at 12 months.

The application also presented a summary of results from phase I pharmacokinetic and dose-finding studies of zanubrutinib (*15*, *16*). Of 37 participants with relapsed/refractory mantle cell lymphoma in the phase I GBG-3111-AU-003 study, 32 (86%) achieved an objective response – 11 with complete response and 21 with partial response (*15*). Median progression-free survival was 15.4 months (*16*).

Direct comparative data of zanubrutinib with other Bruton tyrosine kinase inhibitors for mantle cell lymphoma are lacking. The application presented indirect comparisons of efficacy reported for zanubrutinib (*14*), ibrutinib (*17*, *18*) and acalabrutinib (*19*). Objective response rates were 87% for zanubrutinib, compared with 80% for acalabrutinib and 72% for ibrutinib. Complete response rates were 69% for zanubrutinib, 40% for acalabrutinib and 19–21% for ibrutinib.

Summary of evidence: harms (from the application)

Safety results from phase I and II trials of zanubrutinib were presented (*14*, *15*, *20*).

In study BGB-3111-206, 83/86 (96%) participants experienced at least one adverse event, with most events being grade 1 or 2 in severity; grade 3 and higher adverse events were reported in 34 (40%) participants. The most common haematological adverse events were neutropenia (49%), leukopenia (35%) and thrombocytopenia (33%). The most common non-haematological adverse events were upper respiratory infection (35%) and rash (34%). The most common grade 3 and higher adverse events were neutropenia (20%) and lung infection/pneumonia (9%). In total, 14/86 (16%) participants died during the study, seven within 30 days of the last study treatment (six due to complications of adverse events and one due to disease progression). Seven deaths occurred more than 30 days after the last dose of the study drug; five were due to progressive disease, one was due to complications of a fungal infection of the lungs and one was from unknown cause after receiving three additional lines of therapy (*14*).

From an indirect comparison with ibrutinib in the treatment of relapsed/refractory mantle cell lymphoma, zanubrutinib was associated with a lower incidence of atrial fibrillation (0% versus 6%) and treatment discontinuation due to adverse events (9.3% versus 11%) (*14*, *21*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for treatment of mantle cell lymphoma are not available.

Costs/cost–effectiveness

No cost–effectiveness analysis data for zanubrutinib were presented in the application.

The price for zanubrutinib in the United States is US$ 12 935 per bottle (120 capsules), corresponding to 30 days of treatment at the recommended dose. The price for zanubrutinib in China is ¥ 11 300 per bottle (64 capsules). The monthly treatment cost is ¥ 22 600. Comparatively, the first-generation Bruton tyrosine kinase inhibitor, ibrutinib, is listed in China priced at ¥ 22 680 per month for patients with mantle cell lymphoma.

Availability

Zanubrutinib has regulatory approval from the National Medical Products Administration of the People's Republic of China (2020) and the United States Food and Drug Administration (2019) for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

Regulatory submissions have also been made in Australia, Canada, Europe and Israel.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of zanubrutinib on the EML for treatment of relapsed/refractory mantle cell lymphoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and with short follow-up), important toxicity concerns, high cost and unknown cost–effectiveness.

Zanubrutinib has been recommended as second-line treatment of mantle cell lymphoma in recent guidelines of the National Comprehensive Cancer Network (*8*) and the Chinese Society of Clinical Oncology (*9*).

Committee recommendations

The Expert Committee noted that mantle cell lymphoma is a rare, aggressive variant of non-Hodgkin lymphoma, primarily affecting older people.

The Expert Committee considered the application for inclusion of zanubrutinib on the EML for treatment of relapsed/refractory mantle cell lymphoma was premature. With regard to clinical efficacy, the Committee noted that only phase I and II trial data were currently available, and these are based on a small number of patients and limited follow-up. Data comparing the efficacy and safety of zanubrutinib with other treatments and studies assessing quality of life are also lacking. The Committee noted that zanubrutinib was associated with major haematological toxicity. Overall, the available data were considered insufficient to evaluate the clinical benefit and safety of zanubrutinib as an essential medicine at this time.

The Committee also noted that the cost–effectiveness of zanubrutinib is unknown, and that currently global regulatory approval and availability of zanubrutinib are very limited.

Therefore, the Committee did not recommend inclusion of zanubrutinib on the EML for the treatment of mantle cell lymphoma at this time.

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8.2.3 Immunomodulators

PD-1/PD-L1 immune checkpoint inhibitors – addition – EML

Atezolizumab	**ATC Code: L01FF05**
Durvalumab	**ATC Code: L01FF03**
Nivolumab	**ATC Code: L01FF01**
Pembrolizumab	**ATC Code: L01FF02**

Proposal

Addition of PD-1 and PD-L1 immune checkpoint inhibitors (atezolizumab, durvalumab, nivolumab and pembrolizumab) in the complementary list of the EML for treatment of non-oncogene-addicted locally advanced and metastatic non-small-cell lung cancer (NSCLC).

Applicant

European Society for Medical Oncology (ESMO)

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that the inclusion of immune checkpoint inhibitors for the treatment of NSCLC would have substantial implications for the EML and access to cancer medicines globally. The technical department noted that their clinical effect, ability to address major disease burden at the population level and the accumulation of the existing clinical data would favour their inclusion on the EML. It noted, however, that there were also important concerns that needed to be addressed, such as the establishment of a framework to better inform their selection in national EMLs given the negative implication their inclusion may have on access including inability to safely deliver the treatment, the diversion of resources away from other essential medicines, and the financial hardship for patients who must make out-of-pocket payments. The technical department noted that further data from low- and middle-income countries would help the technical team and Expert Committee better understand the feasibility of the use of immune checkpoint inhibitors for treatment of NSCLC in resource-limited settings and implications of their approval and selection. The technical department concluded that while the inclusion of checkpoint inhibitors for NSCLC may be warranted, strong consideration should be given to the development of such a framework in this review cycle or for the next Expert Committee in 2023.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strength(s)

Atezolizumab: injection 840 mg/14 mL
Durvalumab: injection 120 mg/2.4 mL, 500 mg/10 mL
Nivolumab: injection 10 mg/mL
Pembrolizumab: powder for injection 50 mg

Core/complementary

Complementary

Individual/square box listing

Pembrolizumab with a square box, with atezolizumab, durvalumab and nivolumab as therapeutic alternatives.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

An application for the inclusion of pembrolizumab, nivolumab and atezolizumab on the EML for treatment of patients with metastatic NSCLC was considered by the Expert Committee in 2019. Listing was not recommended as the Committee considered that the precise place of these medicines in the treatment of this condition was still evolving (i.e. immunotherapy alone or in combination with chemotherapy). The Committee noted the evidence of efficacy in the treatment of patients with metastatic NSCLC with these agents. The Committee observed that the duration of follow-up of the single studies for first-line and second-line immunotherapy in trials for lung cancer was generally shorter than 3 years, and considered that data from longer follow-up would better demonstrate the actual magnitude of benefit. The Committee expressed the hope that by the time of the 2021 Committee meeting, more mature data would be available for metastatic NSCLC and also for use of these agents in locally advanced non-resectable disease, and as adjuvant therapy. Furthermore, the Committee noted that the clinical development of cancer immunotherapy still has some areas of uncertainty about the optimal time for introduction of treatment (first- or second-line), appropriate patient selection and whether or not the use of immune checkpoint inhibitors in combination with other medicines is superior to monotherapy. The Committee expressed concern about the potential impact of oncology medicines on budgets, which could be an impediment to access, and the fact that countries may not be able to list these medicines on their national EMLs because of their high price (*1*).

Public health relevance (burden of disease)

Lung cancer is the leading cause of cancer death worldwide, with an estimated 1.7 million related deaths in 2018 (*2*). Lung cancer is a highly lethal malignancy, with an economic impact estimated at around US$ 8 billion in lost productivity in the BRICS countries (Brazil, Russia, India, China, and South Africa). Moreover, in the absence of wide coverage of an effective screening programme in place globally, lung cancer diagnoses occur in advanced stages in more than 60% of cases, with high regional variability (*3–5*).

Over 80% of lung cancers are classified as NSCLC (*6*). Targeted therapies have redefined treatment for patients with genomic alterations in driver oncogenes (e.g. epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase rearrangements, ROS1 rearrangements, BRAF mutations, human epidermal growth factor receptor 2 (HER2) mutations or amplifications and neurotrophic tyrosine kinase (NTRK) 1–3 fusions) to guide the selection of treatments. However, these therapies are ineffective in most patients with NSCLC who have tumours lacking such genetic alterations. Gene-targeted therapies are now estimated to benefit less than 10% of patients with NSCLC, but this proportion might increase rapidly over time (*7*).

Immune checkpoint inhibitor therapy has become part of the standard treatment of patients with advanced and metastatic NSCLC in many high-income settings, based on favourable improvements in clinical outcomes. Immune checkpoint inhibitors target and reactivate immune-competent cells (i.e. T-lymphocytes and antigen-presenting cells) by inhibiting the immunosuppressive ligand PD-L1 or its receptor (PD-1), or by strengthening the immune-activating signals of the immune response (e.g. glucocorticoid-induced tumour necrosis factor receptor-related, proinflammatory interleukins, interferon-gamma) (*8*).

Summary of evidence: benefits (from the application)

First-line monotherapy in metastatic NSCLC expressing high levels of PD-L1

Pembrolizumab

The phase III KEYNOTE-024 study evaluated pembrolizumab as first-line treatment in 500 participants with treatment-naïve, advanced NSCLC showing PD-L1 expression ≥ 50%, in the absence of EGFR mutation or anaplastic lymphoma kinase translocations (non-oncogene-driven NSCLC) (*9*). Participants were randomized to receive 200 mg pembrolizumab every 3 weeks (up to 2 years) or 4–6 cycles of standard platinum-doublet chemotherapy. Efficacy measures favoured pembrolizumab, including progression-free survival (hazard ratio (HR) 0.5, 95% confidence interval (CI) 0.37 to 0.68; $P < 0.001$) and overall survival (HR 0.6, 95% CI 0.41 to 0.89; $P = 0.005$). In the intention-

to-treat population, based on 189 events of progression or death in the first survival report, the median progression-free survival was 10.3 months (95% CI 6.7 months to not reached) in the pembrolizumab group and 6.0 months (95% CI 4.2 to 6.2 months) in the chemotherapy group.

At the time of the second interim analysis, 108 deaths had occurred; 80.2% of participants were alive at 6 months (95% CI 72.9% to 85.7%) in the pembrolizumab group and 72.4% (95% CI 64.5% to 78.9%) in the chemotherapy group. An updated survival report (25.2 months median follow-up) confirmed the superiority of pembrolizumab over chemotherapy: the HR for overall survival was 0.63 (95% CI 0.47 to 0.86; nominal $P = 0.002$), median overall survival was 30.0 months (95% CI 18.3 months to not reached) in the pembrolizumab arm and 14.2 months (95% CI 9.8 to 19.0 months) in the chemotherapy arm; the Kaplan–Meier estimate of overall survival at 12 months was 70.3% (95% CI 62.3% to 76.9%) for the pembrolizumab group and 54.8% (95% CI 46.4% to 62.4%) for the chemotherapy group (*10*). In terms of effect size, pembrolizumab provided a gain of median overall survival of 15.8 months and 15.5% at 1 year.

After more than 3 years of median follow-up, overall survival in participants in the pembrolizumab arm was 26.3 months versus 14.2 months in the chemotherapy arm (*10*). The last data available (5 years follow-up 55.1–68.4 months) indicated that participants treated with pembrolizumab exhibited a consistent and significant overall survival improvement (pembrolizumab 31.9% versus chemotherapy 16.3%) and fewer grade 3–5 adverse events (pembrolizumab 31.2% versus chemotherapy 53.3%) (*11*).

The health-related quality of life analysis showed a clinically meaningful and significant improvement (*12*). Fewer participants treated with pembrolizumab had deterioration in the QLQ-LC13 composite endpoint than participants given chemotherapy (46/151 (31%) versus 58/148 (39%)). Time to deterioration was longer with pembrolizumab than with chemotherapy: median not reached (95% CI 8.5 months to not reached) versus 5.0 months (95% CI 3.6 months to not reached); HR 0.66, 95% CI 0.44–0.97; $P = 0.029$).

Based on the KEYNOTE-024 trial, confirmed at a 3-year follow-up updated survival analysis, pembrolizumab is considered a new standard in several settings as the first-line option for patients with advanced NSCLC and PD-L1 expression ≥ 50% who do not otherwise have contraindications to immune checkpoint inhibitors: grade of evidence and level of recommendation: I, A; European Society for Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 score 5/5.

Participants with PD-L1 ≥ 50% drove the overall survival benefit preponderance, as the only subgroup gaining more than 6 months of overall survival. In comparison, no significant increase in overall survival was seen

in participants with 1%–49% PD-L1 expression in the exploratory analysis of survival, where overall survival was 13.4 versus 12.1 months in this subpopulation (HR 0.92, 95% CI 0.77 to 1.11).

Atezolizumab

The IMpower110 study is a phase III, multicentre trial for untreated non-squamous, non-oncogene addicted metastatic NSCLC in participants whose tumour expressed PD-L1 (*13*). Up to 572 participants were randomized to receive atezolizumab or platinum-based chemotherapy (4 or 6 cycles) once every 3 weeks. At the interim analysis (median follow-up of 15.7 months), atezolizumab monotherapy demonstrated longer overall survival and progression-free survival than the chemotherapy arm. The progression-free survival benefit was respectively 8.1 months versus 5.0 months (stratified HR for disease progression or death, 0.63, 95% CI 0.45 to 0.88). Among participants with EGFR and anaplastic lymphoma kinase wild-type tumours who had high or intermediate PD-L1 expression, progression-free survival was 7.2 months in the atezolizumab group and 5.5 months in the chemotherapy group (stratified HR for disease progression or death 0.67, 95% CI 0.52 to 0.88). The overall survival for atezolizumab compared with chemotherapy arm was respectively 20.2 months versus 13.1 months (HR for death 0.59, 95% CI 0.40 to 0.89; $P = 0.01$) in the population with high PD-L1 expression, according to preplanned interim analysis. As overall survival testing did not meet its threshold in the wild-type population with PD-L1 expression of ≥ 5% by tumour cells or immune-infiltrating cells), overall survival was not tested in this population.

No differences in time to confirmed deterioration were seen between the study arms for cough (HR 0.98, 95% CI 0.48 to 2.03), chest pain (HR 1.02, 95% CI 0.47 to 2.22), dyspnoea (HR 0.96, 95% CI 0.57 to 1.60) and 3-symptom composite score (HR 0.92, 95% CI 0.59 to 1.44). Mean change in physical function from baseline to week 42 was slightly improved with atezolizumab and greater than or similar to chemotherapy. Fatigue and nausea or vomiting scores numerically improved immediately with atezolizumab and were maintained to week 48 (*14*).

Nivolumab

The phase III CheckMate 026 trial included in participants with untreated, advanced NSCLC and PD-L1 ≥ 1%, randomized to nivolumab or platinum-doublet standard chemotherapy (*15*). The trial did not show a superiority of nivolumab over chemotherapy in unselected NSCLC participants. There was no difference in progression-free survival between the treatment groups in the primary efficacy analysis population (participants with a PD-L1 expression ≥ 5%). The median overall survival in the primary efficacy analysis population was 14.4 months (95% CI 11.7 to 17.4 months) in the nivolumab group and

13.2 months (95% CI 10.7 to 17.1 moths) in the chemotherapy group (HR for death 1.02, 95% CI 0.80 to 1.30). Nivolumab was not associated with a longer progression-free survival than chemotherapy.

First-line treatment in combination with cytotoxic chemotherapy in metastatic squamous and non-squamous NSCLC, irrespective of tumour PD-L1 expression

Pembrolizumab

The efficacy and safety of pembrolizumab combined with chemotherapy for untreated advanced non-squamous NSCLC, without sensitizing EGFR/anaplastic lymphoma kinase alterations, regardless of PD-L1 expression, was assessed in the KEYNOTE-189 study (*16*). A total of 616 participants were randomized to receive four cycles of chemotherapy (pemetrexed + platinum-based compound), with pembrolizumab or placebo administered every 3 weeks for up to 35 cycles in a 2:1 ratio. The co-primary endpoints of this study were progression-free survival and overall survival. After a median follow-up of 10.5 months, the study showed a statistically significant progression-free survival improvement in the group treated with pembrolizumab compared with the placebo group: 8.8 months, 95% CI 7.6 to 9.2 months versus 4.9 months, 95% CI 4.7 to 5.5 months; HR for progression or death 0.52, 95% CI 0.43 to 0.64; $P < 0.001$). Likewise, there was a statistically significant improvement in overall survival: not reached versus 11.3 months, 95% CI 8.7 to 15.1 months; HR for death 0.49, 95% CI 0.38 to 0.64; $P < 0.0010$).

Following PD-L1 stratification criteria, the pembrolizumab/chemotherapy arm exhibited efficacy across all subgroups analysed:

- PD-L1 expression < 1%: 12-month overall survival rate 61.7% versus 52.2%; HR for death 0.59, 95% CI 0.38 to 0.92;
- PD-L1 expression 1–49%: 12-month overall survival rate 71.5% versus 50.9%; HR 0.55, 95% CI 0.34 to 0.90; and
- PD-L1 expression ≥ 50%: 12-month overall survival rate 73.0% versus 48.1%; HR 0.42, 95% CI 0.26 to 0.68.

Response rates were also higher in the pembrolizumab combination group: 47.6% (95% CI 42.6% to 52.5%) compared with 18.9% (95% CI 13.8% to 25.0%) in the placebo combination group ($P < 0.001$), and consistent across all PD-L1 subgroups, but notably greater in the subgroup PD-L1 ≥ 50% (61.4% versus 22.9%).

The KEYNOTE-189 update included a median follow-up of 23.1 months (range 18.6 to 30.9 months) and confirmed a sustained clinical and statistically meaningful benefit in efficacy and safety: median overall survival was 22.0 months (rage 19.5 to 25.2 months) in the pembrolizumab combination group and 10.7 months (range 8.7 to 13.6 months) in the placebo combination

group (HR 0.56, 95% CI 0.45 to 0.70), an absolute gain of 10.3 months. The estimated 24-month overall survival rates were 45.5% and 29.9%, respectively. Median progression-free survival was 9.0 months (range 8.1 to 9.9 months) and 4.9 months (range 4.7 to 5.5 months) in the pembrolizumab combination and placebo combination groups, respectively (HR 0.48, 95% CI 0.40 to 0.58), with estimated 24-month progression-free survival rates of 20.5% and 1.5%. Notably, the study update confirmed the benefit for overall survival and progression-free survival across all PD-L1 tumour proportion scores (*17*).

The KEYNOTE-407 trial assessed the efficacy and safety of pembrolizumab plus chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel) compared with placebo plus chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel) in participants with untreated, advanced squamous NSCLC, without sensitizing EGFR/anaplastic lymphoma kinase alterations, and regardless of PD-L1 tumour proportion score (*18*). The median overall survival was 15.9 months (95% CI 13.2 months to not reached) in the pembrolizumab combination group and 11.3 months (95% CI 9.5 to 14.8 months) in the placebo combination group (HR for death 0.64, 95% CI 0.49 to 0.85; $P < 0.001$), and a 1-year Kaplan–Meier estimate of 65.2% in the pembrolizumab arm versus 48.3% in the placebo arm. Overall, the results show an overall survival gain of 4.6 months, reducing death by 36% and favouring the addition of pembrolizumab compared to standard of care chemotherapy. The overall survival benefit extends to all PD-L1 expression subgroups, including PD-L1 < 1%. The progression-free survival benefit was 6.4 months (95% CI 6.2 to 8.3 months) in the pembrolizumab combination group and 4.8 months (95% CI 4.3 to 5.7 months) in the placebo combination group (HR for disease progression or death 0.56, 95% CI 0.45 to 0.70; $P < 0.001$).

First-line consolidation therapy for locally advanced, unresectable NSCLC with PD-L1 expression ≥1%

Durvalumab

The efficacy of durvalumab was evaluated in the PACIFIC trial, a double-blind study in 713 participants with locally advanced, unresectable NSCLC, irrespective of tumour PD-L1 expression (*19*). Participants had completed at least two cycles of definitive platinum-based chemotherapy with radiation therapy within 1 to 42 days before start of the study. Participants were randomized to receive durvalumab (476 participants) or placebo (237 participants) every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. The study showed a significant improvement in progression-free survival in the durvalumab-treated group compared with the placebo group (HR 0.52, 95% CI 0.42 to 0.65; $P < 0.0001$) as well as in overall survival (HR 0.68, 95% CI 0.53 to 0.87; $P = 0.00251$). As of 31 January 2019, 48.2% of the participants had died

(44.1% and 56.5% in the durvalumab and placebo groups, respectively). The median duration of follow-up was 33.3 months. The updated overall survival remained consistent with that previously reported (stratified HR 0.69, 95% CI 0.55 to 0.86). The median overall survival was not reached with durvalumab but was 29.1 months with placebo. The 12-, 24- and 36-month overall survival rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3% and 57.0% versus 43.5%, respectively. All secondary outcomes examined showed improvements consistent with previous analyses (*20*). A significant benefit from durvalumab was observed only in the subgroup with PD-L1 > 1%, both for overall survival (HR 0.53, 95% CI 0.36 to 0.77; median overall survival not reached versus 29.1 months) and progression-free survival (HR 0.46, 95% CI 0.33 to 0.64; median progression-free survival 17.8 versus 5.6 months). In the PD-L1-negative subgroup, no statistically significant improvement was seen in either overall survival (HR 1.36, 95% CI 0.79 to 2.34) or progression-free survival (HR 0.73, 95% CI 0.48 to 1.11).

An exploratory post hoc analysis of outcomes grouped by tumour cell PD-L1 expression from the PACIFIC trial included 709 participants who had received at least one dose of durvalumab (473 participants) or placebo (236 participants) (*21*). After a median follow-up of 33.3 months, durvalumab was associated with a progression-free survival benefit across all PD-L1 expression subgroups, and improved overall survival across all subgroups except PD-L1 < 1%:

- PD-L1 ≥ 25% (HR 0.50, 95% CI 0.30 to 0.83; median not reached versus 21.1 months),
- PD-L1 < 25% (HR 0.89, 95% CI 0.63 to 1.25; median 39.7 versus 37.4 months),
- PD-L1 ≥ 1% (HR 0.59, 95% CI 0.41 to 0.83; median not reached versus 29.6 months),
- PD-L1 1%–24% (HR 0.67, 95% CI 0.41 to 1.10; median 43.3 versus 30.5 months),
- PD-L1 unknown (HR 0.60, 95% CI 0.43 to 0.84; median 44.2 versus 23.5 months),
- PD-L1 < 1% (HR 1.14, 95% CI 0.71 to 1.84; median 33.1 versus 45.6 months).

A recent 4-year overall survival update (20 March 2020, median follow-up 34.2 months (range 0.2–64.9)) confirmed a sustained benefit with durvalumab compared with placebo for progression-free survival (stratified HR 0.55, 95% CI 0.44 to 0.67; median 17.2 versus 5.6 months) and overall survival (stratified HR 0.71, 95% CI 0.57 to 0.88; median 47.5 months versus29.1 months). The

48-month overall survival rates for durvalumab versus placebo were 49.6% versus 36.3% and progression-free survival rates were 35.3% versus 19.5% (*20*, *22*).

Second-line treatment for advanced NSCLC, after failure of platinum-containing standard chemotherapy

Pembrolizumab, nivolumab and atezolizumab have been approved by the United States Food and Drug Administration and the European Medicines Agency for use in the second-line treatment setting, based on phase III studies showing improved overall survival compared with docetaxel (the standard of care in second-line treatment for patients with NSCLC who have not responded to platinum-containing first-line chemotherapy (*23*, *24*). Overall, no major differences were found in efficacy or safety among these three therapies to inform a best single option and no direct comparative studies have been conducted. There are two key distinctions between the three approved therapies, which can affect choice and use.

- *PD-L1 expression in the tumour.* Nivolumab and atezolizumab are approved in patients with previously treated, advanced NSCLC, irrespective of PD-L1 expression, while pembrolizumab is approved only in patients with PD-L1 expression > 1%.
- *Schedule of administration.* Pembrolizumab is approved to be given in the dose of 200 mg every 3 weeks or 400 mg every 6 weeks and nivolumab is approved to be given in the dose of 240 mg once every 2 weeks, whereas atezolizumab can be given in the doses of 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks, based on current approvals by the European Medicines Agency.

Pembrolizumab

The KEYNOTE-010 trial randomized 1033 participants with previously treated squamous and non-squamous NSCLC with PD-L1 expression of at least 1% to receive pembrolizumab (tested at two doses, 2 mg/kg or 10 mg/kg, every 3 weeks) or docetaxel (75 mg/m² every 3 weeks) (*25*). Overall survival was longer for the pembrolizumab group than the docetaxel group: 2 mg/kg (HR 0.71, 95% CI 0.58 to 0.88; $P < 0.001$); 10 mg/kg (HR 0.61, 95% CI 0.49 to 0.75; $P < 0.001$), with a 2-year overall survival rate of 14.5% versus 30.1% (2 mg/kg group).

Median overall survival was 14.9–17.3 for the 2 mg/kg and 10 mg/kg arms, compared with 8.2 months for the chemotherapy arm. The safety profile favoured pembrolizumab with a smaller percentage of participants with grade 3–5 adverse events (16%) than in the chemotherapy arm (35%), and decreased appetite (14%) and fatigue (14%) for immune checkpoint inhibitors, and neutropenia (14%), alopecia (33%), anaemia (13%) and oral mucositis (14%) for

chemotherapy. No relevant differences in the safety of pembrolizumab were seen between participants given 2 mg/kg or 10 mg/kg.

Long-term outcomes from KEYNOTE-010 were recently published (*26*). Pembrolizumab continued to show improved overall survival compared with docetaxel in the PD-L1 ≥ 50% and PD-L1 ≥ 1% groups (HR 0.53, 95% CI 0.42 to 0.66; $P < 0.00001$ and HR 0.69, 95% CI 0.60 to 0.80; $P < 0.00001$, respectively) after a 42.6-month median follow-up. Estimated 36-month overall survival rates for PD-L1 expression ≥ 50% and PD-L1 expression ≥ 1% groups were 34.5% (pembrolizumab) versus 12.7% (docetaxel) and 22.9% versus 11.0%, respectively. Grade 3–5 treatment-related adverse events occurred in 16% versus 37% of participants in the pembrolizumab and docetaxel groups, respectively. Of 690 participants, 79 completed 35 cycles per 2 years of pembrolizumab: 12-month overall survival and progression-free survival rates after completing treatment were 98.7% (95% CI 91.1% to 99.8%) and 72.5% (95% CI 59.9% to 81.8%), respectively.

Nivolumab

In the CheckMate-017 trial, 272 participants with squamous NSCLC were randomized to receive nivolumab or docetaxel (*27*). The median overall survival was 9.2 months (95% CI 7.3 to 13.3 months) in the nivolumab group and 6.0 months (95% CI 5.1 to 7.3 months) in the docetaxel group. In the CheckMate-057 trial, 582 participants with non-squamous NSCLC (e.g. adenocarcinoma) were randomized to nivolumab or docetaxel (*28*).

In a recent update of the CheckMate-017 and CheckMate-057 trials, the pooled 2-year overall survival favoured nivolumab in both squamous NSCLC (29%, 95% CI 24% to 34% versus 16%, 95% CI 12% to 20%) and non-squamous NSCLC (23%, 95% CI 16% to 30% versus 8%, 95% CI 4% to 13%) (*29*). In the pooled analysis of overall survival in the intention-to- treat population (854 participants) with squamous (272 participants (31.9%)) and non-squamous (582 (68.1%)) NSCLC, median overall survival was 11.1 months (95% CI 9.2 to 13.1 months) with nivolumab versus 8.1 months (95% CI 7.2 to 9.2 months) with docetaxel (HR 0.72, 95% CI 0.62 to 0.84). Higher PD-L1 expression levels were associated with greater overall survival benefit with nivolumab (HR 0.42, 95% CI 0.28 to 0.63) in participants with PD-L1 ≥ 50%, but a benefit was still observed in participants with PD-L1 < 1% (HR 0.78, 95% CI, 0.61 to 0.99). Consistent with the primary analyses, nivolumab showed a better 2-year overall survival benefit than docetaxel in participants with squamous NSCLC regardless of PD-L1 expression level. However, in participants with non-squamous NSCLC, higher levels of PD-L1 were associated with a greater overall survival benefit with nivolumab, but NSCLC patients with PD-L1 < 1% still derived greater benefit from immune checkpoint inhibitors than chemotherapy: in participants with PD-L1 ≥ 50%, the HR for overall survival

on the basis of 2 years minimum follow-up was 0.38 (95% CI 0.24 to 0.60) for participants with non-squamous NSCLC.

Pooled data from four clinical studies of nivolumab in participants with previously treated NSCLC (CheckMate 017, 057, 063 and 003) showed 4-year overall survival with nivolumab was 14% for all participants (664 participants), 19% for those with PD-L1 expression > 1% and 11% for those with PD-L1 expression < 1%. Nivolumab continued to show long-term overall survival and progression-free survival benefit compared with docetaxel, with 5-year survival rates of 13.4% versus 2.6% and progression-free survival rates of 8% versus 0%. Survival after a response at 6 months on nivolumab or docetaxel was longer than after progressive disease at 6 months: HR for overall survival 0.18 (95% CI 0.12 to 0.27) for nivolumab and HR 0.43 (95% CI 0.29 to 0.65) for docetaxel. For stable disease versus progressive disease, HR for overall survival was 0.52 (95% CI 0.37 to 0.71) for nivolumab and HR 0.80 (95% CI 0.61 to 1.04) for docetaxel. Long-term data did not show any new safety signals (*30*).

Atezolizumab

The phase III OAK trial evaluated atezolizumab versus docetaxel in 850 participants with previously treated, advanced squamous and non-squamous NSCLC (*31*). Overall survival was improved in participants given atezolizumab (median overall survival 13.8 months, 95% CI 11.8 to15.7 months) compared with participants given docetaxel (9.6 months, 95% CI 8.6 to 11.2 months), with HR 0.73 (95% CI 0.62 to 0.87; $P = 0.0003$). Subgroup analysis showed a greater magnitude of benefit in patients with higher PD-L1 expression, both assessed on tumour cells or immune-infiltrating cells: the net benefit gain with tumour cells 1/2/3 or immune-infiltrating cells 1/2/3 was +5.4 months (HR 0.74, 95% CI 0.58 to 0.93; $P = 0.0102$) and +5.5 months with tumour cells 2/3 or immune-infiltrating cells 2/3 (HR 0.67, 95% CI 0.49 to 0.90; $P = 0.0080$). Data for patient-reported outcomes in the OAK study found that atezolizumab delayed the time to deterioration in patient physical function and role function compared with docetaxel. No significant differences in time to deterioration were observed between treatment arms for health-related quality of life, although the point estimate numerically favoured atezolizumab (HR 0.94, 95% CI 0.72 to 1.24) (*32*).

Summary of evidence: harms (from the application)

Pembrolizumab

In Keynote-024, treatment-related adverse events occurred in 73.4% of participants in the pembrolizumab group and 90.0% of participants in the chemotherapy group. In the pembrolizumab and chemotherapy groups respectively, 26.6% and 53.3% of adverse events were grade 3 (moderate-severe) to grade 5 (toxic death), which resulted in a higher treatment discontinuation rate because of these adverse events in the chemotherapy group (10.7% versus

7.1%). Despite longer mean treatment duration in the pembrolizumab group (11.1 versus 4.4 months), grade 3–5 treatment-related adverse events were less frequent with pembrolizumab than chemotherapy after 3 years follow-up (*10*). The most common treatment-related adverse events in the pembrolizumab arm were hypo- and hyperthyroidism (in 9% and 8% of participants, all grade 1 and 2), diarrhoea (in 14.3%), fatigue (in 10.4%) and pyrexia (in 10.4%). For chemotherapy, bone marrow toxicity (anaemia in 44.0%) and traditional systemic treatment-related adverse events were observed (nausea in 43.3% and fatigue in 28.7%); anti-emetic premedication was allowed per protocol, consistent with institutional and international guidelines for moderately to highly emetogenic platinum-containing chemotherapy regimens in the standard of care arm.

The most frequent adverse events in the KEYNOTE-189 trial were nausea (55.6% in the pembrolizumab arm versus 52% in the placebo arm, grade 3 in 3.5% in both arms), anaemia (46.2% versus 46.5%, grade ≥ 3 in 16.3% versus 15.3%), fatigue (40.7% versus 38.1%, grade ≥ 3 in 5.7% versus 2.5%). Rates of treatment-related adverse events were similar for carboplatin and cisplatin. The proportion of participants who discontinued all trial drugs because of treatment-related adverse events was greater in the pembrolizumab arm than the placebo arm (13.8% versus 7.9%). Overall, the immune-related treatment-related adverse events of interest occurred in the pembrolizumab arm (any grade, 22.7%; grade ≥ 3, 8.9%) or placebo (any grade, 11.9%; grade 3, 4.5%) group. The most frequent immune-related treatment-related adverse events in the pembrolizumab arm were hypothyroidism (any grade, 6.7%; grade ≥ 3, 0.5%), pneumonitis (any grade, 4.4%; grade 3, 2.7%), hyperthyroidism (any grade, 4%; grade ≥ 3, 0%), infusion reaction (any grade, 2.5%; grade ≥ 3, 0.2%), and colitis (any grade, 2.2%; grade 3, 0.7%) (*17*).

In the KEYNOTE-407 trial of pembrolizumab in combination with chemotherapy, 98.2% of participants in the pembrolizumab arm versus 97.9% in the placebo arm experienced any grade of treatment-related adverse events, where anaemia, alopecia and neutropenia were the most common in both arms. Treatment-related adverse events of grade ≥ 3 occurred in 69.8% of participants in the pembrolizumab arm and 68.2% in the placebo arm; anaemia and neutropenia occurred in more than 10% of the participants. Pneumonitis and autoimmune hepatitis were the grade ≥ 3 adverse events that occurred more frequently in the pembrolizumab arm, with percentages similar to those observed in the KEYNOTE-189 trial (*18*).

Atezolizumab

In the IMpower110 Study, treatment-related adverse events occurred in both the atezolizumab and chemotherapy arms: any grade in 90.2% of participants in the atezolizumab arm versus 94.7% of participants in the chemotherapy

arm; grade 3 and 4 in 30.1% versus 52.5%; and grade 5 in 3.8% versus 4.2%. The most frequent grade 3 and 4 adverse events were anaemia, neutropenia and thrombocytopenia. Hepatic laboratory abnormalities, rash and hypothyroidism were the most reported immune-mediated treatment-related adverse events (≥ 5% in both groups). Grade 3 or 4 immune-mediated treatment-related adverse events occurred in 6.6% of participants in the atezolizumab arm and 1.5% in the chemotherapy arm, with no grade 5 event reported (*13*). For patient-reported outcomes in the OAK study, fewer participants receiving atezolizumab experienced grade 3 or 4 treatment-related adverse events (14.9%) than did participants receiving docetaxel (42.4%); no grade 5 treatment-related adverse events related to atezolizumab were observed (*32*).

Durvalumab

In the PACIFIC study, the most frequent treatment-related adverse events were cough (40.2% in the durvalumab arm versus 30.3% in placebo), upper respiratory tract infections (26.1% versus 11.5%) and rash (21.7% versus 12.0%). The most frequent grade 3–4 treatment-related adverse event was pneumonia (6.5% versus 5.6%). The overall incidence of grade 3 or 4 treatment-related adverse events was 12.8% in the durvalumab arm and 9.8% in the placebo arm (*19*). Overall, durvalumab is most associated with immune-mediated treatment-related adverse events. In the combined safety database with durvalumab monotherapy (1889 participants with multiple tumours types), immune-mediated pneumonitis occurred in 79 (4.2%) participants, including grade 3 in 12 participants (0.6%), grade 4 in one patient (< 0.1%) and grade 5 in five participants (0.3%). Durvalumab does not induce antibody-dependent cell-mediated cytotoxicity.

Other immune-related treatment-related adverse events reported in less than 1% of participants treated with durvalumab monotherapy in clinical trials were myasthenia gravis, myocarditis, myositis, polymyositis, meningitis, encephalitis and Guillain–Barre syndrome. No overall differences in safety were reported between elderly (≥ 65 years) and younger participants.

Preliminary real-world data of durvalumab consolidation after chemoradiotherapy compared with regular follow-up after chemoradiotherapy found the incidence of grade 3 radiation pneumonitis was higher in the group treated with durvalumab (14.3% versus 2.5%) (*33*).

Nivolumab

In the CheckMate-017 trial in patients with squamous NSCLC, treatment-related adverse events, including hematologic and non-haematological events, occurred less frequently with nivolumab than with docetaxel: in the nivolumab group, 58% of participants had events of any grade, of which 7% were grade 3 or 4; in the docetaxel group, 86% of participants had events of any grade, of which 55% were grade 3 or 4. The safety profile was consistent

with the class side-effects with no new signals of safety. The most frequently reported treatment-related adverse events with nivolumab were fatigue and asthenia, and for docetaxel were neutropenia (33%); 10% febrile neutropenia), fatigue (33%), alopecia (22%), nausea (23%) and peripheral neuropathy (11%). Treatment discontinuations due to adverse events were reported in 3% and 10% of participants in the nivolumab and chemotherapy arms, respectively (*27*). In the CheckMate-057 trial, the safety profile and pattern of adverse events in participants with non-squamous NSCLC were consistent with the data from the participants with squamous NSCLC. Treatment-related adverse events of any grade were observed in 69% and 88% of participants in the nivolumab and docetaxel arms, respectively. Grade 3–4 adverse events were observed in 10% of participants in the nivolumab arm and 54% of participants in the docetaxel arm. Discontinuation rates were 5% in the nivolumab arm and 15% in the docetaxel arm (*28*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for treatment of NSCLC are not currently available.

The ESMO clinical practice guidelines for metastatic non-small-cell lung cancer (last updated in September 2020) include the following recommendations (*34*).

First-line treatment of EGFR- and anaplastic lymphoma kinase-negative NSCLC, PD-L1 ≥ 50%

> Pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression ≥ 50% who do not otherwise have contraindications to use of immunotherapy (such as severe autoimmune disease or organ transplantation) [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 5].
>
> Atezolizumab represents a promising first-line treatment option in patients with PD-L1-high (following the specific definition of TC3 or IC3 per trial design) NSCLC [I, A; not EMA-approved], with the formal caution of a subgroup analysis compared with trial design and ITT using only TC > 50% [I, B].

First-line treatment of EGFR- and anaplastic lymphoma kinase-negative NSCLC, regardless of PD-L1 status

> Based on the results from KEYNOTE-189, pembrolizumab in combination with pemetrexed and a platinum-based ChT [chemotherapy] should be considered a standard option in metastatic non-squamous NSCLC [I, A; ESMO-MCBS v1.1 score: 4].

Results from KEYNOTE-407 place the combination of pembrolizumab plus carboplatin and paclitaxel or nab-P [nab-paclitaxel] as a standard choice in patients with metastatic squamous NSCLC [I, A; ESMOMCBS v1.1 score: 4].

Second-line treatment of NSCLC without actionable oncogenic driver

Pembrolizumab, atezolizumab and nivolumab "represent reasonable standard therapy for most patients with advanced, previously treated, PD-L1-naïve NSCLC" [I, A; ESMO-MCBS v1.1 score: 5].

First-line consolidation therapy for locally advanced, unresectable NSCLC with PD-L1 expression ≥ 1%

ESMO clinical practice guidelines for early-stage and locally advanced (non-metastatic) non-small-cell lung cancer (last updated May 2020) (*35*) recommend consolidation administration of durvalumab in patients with unresectable stage III NSCLC with PD-L1 ≥ 1% and whose disease has not progressed following platinum-based chemoradiotherapy [I, A; ESMO-MCBS v1.1 score: 4].

Costs/cost–effectiveness

A cost–effectiveness analysis of pembrolizumab as first-line treatment in patients with high PD-L1 expression was conducted using data from Keynote 024, from the perspective of a United States third-party public health care payer (*36*). Pembrolizumab would be expected to result in an incremental cost of US$ 98 281 per quality-adjusted life year (QALY) gained or an incremental cost of US$ 78 873 per life year gained. Including the cost of PD-L1 testing had a very small effect on the model results. With a 5-year time horizon, the ICER was US$ 99 998/LY and US$ 122 024/QALY; with a 10-year time horizon, the incremental cost–effectiveness ratio was US$ 83 065/life year and US$ 103 101/QALY. Base-case results indicated that, compared with standard of care over a 20-year time horizon, pembrolizumab would be expected to result in an additional 1.31 life years gained and an additional 1.05 QALYs gained.

For pembrolizumab in combination with chemotherapy for first-line treatment of metastatic non-squamous NSCLC, the National Institute for Health and Care Excellence (NICE) technology appraisal guidance (TA557, 10 Jan 2019) calculated that the incremental cost–effectiveness ratio was less than £ 50 000 per QALY gained and concluded that incremental cost–effectiveness ratios were not all clearly within the range usually considered a cost-effective use of resources. At that time, NICE decided not to recommend pembrolizumab combination for routine use in adults with untreated, metastatic, non-squamous NSCLC whose tumours have no EGFR- or anaplastic lymphoma kinase-positive mutations (*37*). Updated guidance (TA683, 10 March 2021), considering updated overall survival data, concluded that the most plausible estimates of cost–effectiveness for pertuzumab in combination with chemotherapy were

within what NICE considers a cost-effective use of resources and recommended the combination as an option for untreated, metastatic non-squamous NSCLC with a 2-year stopping rule (*38*).

For pembrolizumab in combination with chemotherapy for first-line treatment of metastatic squamous NSCLC, NICE technology appraisal guidance (TA600, 11 Sept 2019) concluded that the long-term overall survival benefit with pembrolizumab combination therapy was uncertain because of the very short duration of the interim data from KEYNOTE-407. The committee decided that the incremental cost–effectiveness ratio was not within the range usually considered a cost-effective use of resources and that further overall survival data are required to reduce cost–effectiveness uncertainty (*39*).

A decision-analytic microsimulation model was developed to compare chemoradiotherapy with chemoradiotherapy followed by durvalumab consolidation therapy until progression or a maximum of 1 year for potential budgetary consequences. Among 2 million simulated patients, durvalumab consolidation therapy was cost-effective compared with no consolidation therapy at a willingness-to-pay threshold of US$ 100 000 per QALY, with an estimated incremental cost–effectiveness ratio of US$ 67 421 per QALY. Durvalumab consolidation therapy would contribute an additional US$ 768 million to national cancer spending in the first year, decreasing to US$ 241 million in year 5. Durvalumab consolidation therapy indicates that expensive immunotherapies can be cost-effective because treating with immunotherapy earlier during cancer progression can provide significant value, despite having a substantial budgetary consequence (*40*).

In another study, a Markov model based on the 3-year follow-up data of the PACIFIC trial was used to compare consolidation durvalumab with observation, using published utility values. The study assessed costs for treatment strategies from the perspective of the Swiss health care payers. In the unselected and PD-L1-positive patients, durvalumab showed incremental effectiveness ratios of Sw.fr. 88 703 per QALY gained and Sw.fr. 66 131 per QALY gained, respectively. Durvalumab was cost-effective at a willingness-to-pay threshold of Sw.fr. 100 000 per QALY gained in almost three quarters of simulations in the probabilistic sensitivity analysis (*41*).

For durvalumab as consolidation therapy after platinum-based chemoradiation in locally advanced unresectable NSCLC, NICE technology appraisal guidance (TA578, 1 May 2019) noted that durvalumab had the potential to be cost-effective compared with standard care, but more evidence from the ongoing PACIFIC trial was needed to address uncertainties associated with the duration of treatment effect and the rate of disease progression (*42*).

Some pharmaceutical manufacturers have set up access programmes to facilitate availability of checkpoint inhibitors in low- and middle-income countries. However, few details are available in the public domain on the exact

characteristics of these programmes, including tiered pricing strategies, or on the effect of these programmes on equitable access and affordability.

Availability

Pembrolizumab (trade name Keytruda, Merck), atezolizumab (trade name Tecentriq, Genetech) and nivolumab (trade name Opdivo, Bristol Myers Squibb) have regulatory approval in multiple countries for the treatment of metastatic NSCLC. They have primary patent protection until 2028, 2029 and 2026, respectively.

Durvalumab (trade name Imfinzi, AstraZeneca) has regulatory approval in multiple countries for the treatment of locally advanced, unresectable NSCLC as consolidation therapy after platinum-based chemotherapy. It has primary patent protection until 2030.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the inclusion of pembrolizumab on the EML for first-line treatment of metastatic NSCLC in selected patients with PD-L1 expression ≥ 50% based on evidence of a relevant and meaningful survival benefit. Considering the other PD-1/PD-L1 monoclonal antibodies, atezolizumab has also shown evidence of benefit in this setting (first-line, PD-L1 expression ≥ 50%), but the data are not as robust as they are for pembrolizumab. Recent meta-analyses suggest, however, similar performance of the different PD-1/PD-L1 antibodies (*43*, *44*), so other monoclonal antibodies within the same class could be considered as possible alternatives for selection at the country level to provide opportunities for better procurement and tendering.

The Working Group did not support the listing at this time of PD-1/PD-L1 immune checkpoint inhibitors for use in stage 3 locally advanced disease, second-line in the metastatic setting, or as maintenance therapy.

Regarding cost–effectiveness, the Working Group noted that cost–effectiveness has not been proven using the list prices available in countries, but rather at discounted prices negotiated with health system payers. The effect on health system budgets of supplying these treatments will be very high in many countries. Weight-based dosing of pembrolizumab (2 mg/kg) may be preferred over fixed dosing because it is less costly, and without loss of benefit.

Molecular and immunohistochemistry diagnosis is a vital component for using immunotherapy in NSCLC and involves at least PD-L1 staining, and analysis of EGFR and anaplastic lymphoma kinase.

Validated immunohistochemistry companion tests defined for the regimens described are available. The authors of a recent study validating the three different available biomarkers for NSCLC (22C3, SP263 and

SP142), asserted that their study "consolidates the analytical evidence for interchangeability of the 22C3, 28-8, and SP263 assays and lower sensitivity of the SP142 assay" (*45*).

To address the feasibility of adopting the regimens mentioned above, the following factors need to be evaluated: the existing and required workforce and their expertise; capacity-building standards; governance for access to the medicines' chain; and the financial aspects of offering timely, high-quality, accurate and reliable pathology diagnosis and treatment without catastrophic or excessive expenditure for the patient or health system.

Committee recommendations

The Expert Committee acknowledged the treatment of lung cancer to be complex and recognized the need to provide the best available care within the context of both non-small-cell lung cancers (NSCLC) and small-cell lung cancers. Over the past decade, the treatment regimen for advanced NSCLC has progressed favourably with new treatment regimens involving targeted therapy based on the molecular and biological characteristics of the cancer. For NSCLC with mutation in the epidermal growth factor receptor (EGFR), the Committee recalled the recommendations made in 2019 to include erlotinib, gefitinib and afatinib as therapeutic alternatives for this indication. These medicines are associated with improved quality of life, and prolonged overall survival compared with cytotoxic chemotherapy, in patients with the EGFR driver mutation.

The Committee noted that more than 80% of lung cancers are classified as non-small-cell and 15–25% of those cancers have programmed cell death ligand 1 (PD-L1) proteins on the surface of their cells. The Committee acknowledged that immune checkpoint inhibitors – PD-1 and PD-L1 inhibitors – have substantially improved outcomes of NSCLC treatment. Clinical trials with these agents have shown rapid and durable responses in about one fifth of pretreated patients with advanced NSCLC. Even though progression-free survival figures are not impressive, survival outcomes are remarkable. Immune checkpoint inhibitors are associated with a relevant survival benefit well over the established EML threshold for survival (i.e. 4 to 6 months) as first-line treatment in several single studies. The benefit from the checkpoint inhibitors was mostly restricted to patients with PD-L1-positive tumours. Addition of immune checkpoint inhibitors to conventional chemotherapy was associated with a modest increase in toxicity, which may require highly specialized management in selected cases.

The Committee noted that even though procurement agencies in some countries have commercial arrangements to obtain a discount on the dose price of PD-1 and PD-L1 inhibitors, the overall price remains very high. The size

of the discount varies and is not disclosed publicly in many settings. In best scenarios, the price is around US$ 45 000 per year of treatment, a price that exceeds the median annual household income of even the richest countries and is largely unaffordable in most settings. The high prices, coupled with the significant disease burden and the likely large eligible patient population, will have unsustainable financial implications for many patients and health systems.

The costs associated with treatment are complicated by variable and the less remarkable response rate for NSCLC with PD-L1 expression less than 50% as compared with NSCLC with PD-L1 expression greater than 50%, and the uncertainties about the optimal duration of treatment. Some health care systems are adopting a 2-year stopping rule for checkpoint inhibitors. This rule assumes that, if the disease has not worsened, this treatment will provide a lasting, life-time survival benefit. The Committee noted that the duration of any continued treatment effect is unknown, and it is possible that life-time survival benefit can be equally obtained with shorter duration of treatment. There might be resistance from physicians and patients benefiting from treatment to stopping the treatment, which could expose health care systems and/or patients to a substantial economic burden that could severely damage national and/or family budgets. As part of a broader strategy to make these highly priced medicines more accessible and affordable, the Committee would value strategic trials to determine the optimal length of treatment required for these patients or to identify subgroups in whom treatment can be safely shortened.

The Committee considered that the use of PD1 and PD-L1 immune checkpoint inhibitors in settings where non-squamous NSCLC is often diagnosed late and there is an underutilization of pretreatment testing to measure PD-L1 expression for predicting a response to immunotherapies might be associated with unintended and harmful consequences.

Overall, the Committee considered that the PD-1/PD-L1 immune checkpoint inhibitors to have a favourable benefit-to-harm ratio in treatment of NSCLC, but recommended that they should not be added to the EML at this time due the prohibitively high price of these medicines.

The Committee noted that several monoclonal antibodies directed at the PD-1 receptor (e.g. nivolumab, pembrolizumab and pidilizumab) or its ligand PD-L1 (e.g. atezolizumab, durvalumab and avelumab) are used in clinical practice, and others are in different stages of clinical development. The Committee recognized the important role of immune checkpoint inhibitors as a therapeutic class in the treatment of NSCLC. It advised that it would welcome a comprehensive review of all available immune checkpoint inhibitors used in the treatment of NSCLC, providing data on duration of therapy, for consideration by the Expert Committee in 2023. The Committee noted that data on the optimal duration of treatment are likely to consolidate over the next 2 years.

The Committee also considered that immune checkpoint inhibitors could be flagged to the Medicines Patent Pool as candidates for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this class of medicines in low- and middle-income countries. In addition, the Committee noted that WHO prequalification processes for monoclonal antibodies for cancer has resulted in prequalification of two molecules – rituximab and trastuzumab. The Committee considered that immune checkpoint inhibitors would also be candidates for WHO prequalification, to facilitate access to affordable and quality-assured products. The Committee considered that WHO prequalification and voluntary licence agreements are key actions that could facilitate the current regulatory pathways for approval of daratumumab, either originator or biosimilar, at the country level.

The Committee also recommended that the high price of PD1 and PD-L1 immune checkpoint inhibitors could be a priority for the proposed EML Working Group addressing pricing and competition issues.

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Daratumumab – addition – EML

Daratumumab — ATC Code: L01FC01

Proposal

Addition of daratumumab to the complementary list of the EML for the treatment of newly diagnosed and relapsed or refractory multiple myeloma in transplant-eligible and transplant-ineligible settings.

Applicant

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Cochrane Cancer and Cochrane Haematology

WHO technical department

Comments were received from the WHO Department Noncommunicable Diseases. The technical department advised that while there were some data to support daratumumab's clinical value, there are insufficient mature overall survival data available to fully justify its inclusion in the EML. Furthermore, the toxicity profile must also be considered.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strength(s)

Injection: 100 mg/5 mL, 400 mg/20 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Daratumumab had not previously been considered for inclusion in the EML.

Other medicines for the treatment of multiple myeloma were reviewed by the Expert Committee in 2019. The Committee acknowledged the treatment

of multiple myeloma to be complex and recognized the need to provide the best available care within the context of both non-transplant and transplant settings. The Committee recommended the addition of bortezomib, lenalidomide and thalidomide to the complementary list of the EML for treatment of multiple myeloma in both non-transplant and transplant eligible/available settings based on good evidence showing large improvements in survival outcomes with acceptable safety for patients with newly diagnosed multiple myeloma.

Concerning treatment of multiple myeloma in transplant-eligible populations, the Committee noted the additional evidence presented supporting standard regimens used in the induction phase before autologous stem cell transplantation, which involved three-drug combinations: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone) and RVD (lenalidomide, bortezomib, dexamethasone). The Committee also noted the benefit of lenalidomide maintenance therapy following autologous stem cell transplantation. In the non-transplant setting, the Committee acknowledged that the proposed medicines are administered as part of treatment regimens including companion cytotoxic agents and/or steroids (melphalan, cyclophosphamide, prednisone and dexamethasone). Accordingly, the Committee recommended the addition of melphalan to the complementary list of the EML for treatment of multiple myeloma, and that the current listings for cyclophosphamide, doxorubicin, prednisone and dexamethasone be extended to include multiple myeloma as an indication (*1*).

Public health relevance (burden of disease)

Multiple myeloma is the second most common haematological cancer with an estimated 176 404 cases and 117 077 deaths worldwide in 2020. In 2020, the age-standardized incidence and mortality rates were 1.9 per 100 000 population and 1.1 per 100 000 population, respectively (*2*). Between 1990 and 2016, the incidence increased by 126% worldwide, with the largest increase observed in low- and middle-income countries. Incidence is strongly associated with age (*3*, *4*).

In high-income countries, autologous stem cell transplantation is routinely used for younger patients with a good general state of health. However, autologous stem cell transplantation is not available in many low- and middle-income countries (*3*). Lack of access to general and specialized health care has led to wide disparities in survival rates between high- and low/middle-income countries. In the United Kingdom of Great Britain and Northern Ireland, 52.3% of patients diagnosed with multiple myeloma are predicted to survive at least 5 years and 29.1% at least 10 years (*4*). In comparison, a 5-year survival rate of only 7.6% was reported in Nigeria in a multicentre retrospective study from

2003 to 2012 (*5*), and of 15.5% in Ghana in a single-centre retrospective study from 2002 to 2016 (*6*).

Summary of evidence: benefits (from the application)

Transplant-ineligible newly diagnosed multiple myeloma

A Cochrane systematic review (in development) evaluated the efficacy and safety of daratumumab in addition to antineoplastic therapy compared with antineoplastic therapy alone in adults with newly diagnosed multiple myeloma who were ineligible for transplant (*7*). The review included two randomized controlled trials (ALCYONE (*8*) and MAIA (*9*), 1443 participants). The overall risk of bias was judged to be high for survival outcomes and quality of life. Median survival was not reached in either group in both studies.

The systematic review found moderate-certainty evidence that treatment with daratumumab probably increases overall survival compared with treatment without daratumumab (hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.5 to 0.85). The magnitude of clinical benefit could not be graded for survival because median survival had not yet been reached in either trial.

There was moderate-certainty evidence that treatment with daratumumab probably increases progression-free survival compared with treatment without daratumumab (HR 0.48, 95% CI 0.36 to 0.63). The magnitude of clinical benefit was graded as 4 out of 4 (progression-free survival benefit compared to comparator HR < 0.65 and estimated progression-free survival gain > 3 months), using the European Society for Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1.

Quality of life was assessed in both trials using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) on a scale of 0 to 100. An increase or decrease from baseline of at least 10 points of global health status was classified as clinically relevant. An increase of at least 10 points was reported for 59.7% of patients in the daratumumab groups and 53.1% of patients in the control groups. Moderate-certainty evidence suggests that more people receiving daratumumab probably gain at least 10 points of global health status after start of treatment compared with people receiving no daratumumab (risk ratio (RR) 1.13, 95% CI 1.13 to 1.23). A decrease of at least 10 points was reported for 38.4% of patients in the daratumumab groups and 37.9% of patients in the control groups. Moderate-certainty evidence suggests that impairment of at least 10 points of global health status at 9 months after start of treatment is probably similar for patients in both groups (RR 1.02, 95% CI 0.89 to 1.16).

Transplant-eligible newly diagnosed multiple myeloma

Two randomized controlled trials (1744 participants) compared daratumumab with active controls in transplant-eligible participants with newly diagnosed multiple myeloma – CASSIOPEIA (*10*) and GRIFFIN (*11*).

The CASSIOPEIA study reported overall survival after median follow-up of 18.8 months for 1085 participants. Fourteen participants (2.6%) in the daratumumab group and 32 participants (5.9%) in the control group had died. Median survival was not reached in either group. There is low-certainty evidence that treatment with daratumumab may increase overall survival compared with control (HR 0.52, 95% CI 0.33 to 0.82). The magnitude of clinical benefit could not be graded for overall survival because median survival had not yet been reached in either trial.

Median progression-free survival was not reached in either group of both studies (1292 participants). In the CASSIOPEIA trial, at data cut off in May 2019, 79 events (14.5%) of disease progression occurred in the daratumumab group compared with 136 events (25.1%) in the control group. In the GRIFFIN trial, at median follow-up of 22.1 months, four (3.8%) and seven (6.8%) disease-progression events had occurred in the daratumumab and control groups, respectively. There was very-low-certainty evidence that daratumumab treatment may increase progression-free survival compared with control treatment (HR 0.49, 95% CI 0.36 to 0.68). The magnitude of clinical benefit could not be graded for progression-free survival because median progression-free survival was not yet reached in either trial.

Quality of life was assessed in the CASSIOPEIA trial after up to 9 months of treatment using the EORTC QLQ-C30. An increase in the global health status from baseline by at least 10 points was reported for 38.1% of participants in the daratumumab group and 35.8% in the control group. There was low-certainty evidence that more people receiving daratumumab treatment may gain at least 10 points of global health status compared with those on control treatment (RR 1.07, 95% CI 0.91 to 1.24). A decrease of at least 10 points was reported for 22.1% of participants in the daratumumab group and 25.6% of participants in the control group. There was low-certainty evidence that fewer participants receiving daratumumab compared with control may have a decline of at least 10 points of global health status (RR 0.86, 95% CI 0.70 to 1.07).

Relapsed or refractory multiple myeloma

Results from four randomized controlled trials (CANDOR (*12*), CASTOR (*13*), LEPUS (*14*) and POLLUX (*15*); 1308 participants) comparing daratumumab with active controls in participants with relapsed or refractory multiple myeloma were included in a rapid evidence synthesis.

The four studies reported overall survival for 1717 participants. Median survival was not reached in either group of the four studies. In the CANDOR

trial, 59 participants (19%) died in the daratumumab group and 36 (23%) in the control group at data cut-off in July 2019. In the CASTOR trial, 102 (42.5%) deaths in the daratumumab group and 119 (50.9%) deaths in the control group occurred at the time of analysis in October 2018. The LEPUS trial reported 13 (9%) deaths in the daratumumab group and 18 (26%) deaths in the control group after a median follow-up of 8.2 months (range 0 to 20.5 months). In the POLLUX trial, 104 (37.0%) deaths had occurred in the daratumumab group and 121 (43.8%) deaths in the control group, at a median observation time of 17.3 months (95% CI 17.0 to 17.8) in both groups. There was moderate-certainty evidence that daratumumab treatment probably increases overall survival compared with control treatment (HR 0.62, 95% CI 0.49 to 0.79). The magnitude of clinical benefit could not be graded for overall survival because median survival had not yet been reached in any of the trials.

The four studies reported progression-free survival for 1744 participants. In the CANDOR trial, median progression-free survival was not reached in the daratumumab group and was 15.8 months (95% CI 12.10 months to not estimable) in the control group. After a median follow-up time for progression-free survival of 16.9 months in the daratumumab group and 16.3 months in the control group, 110 (35%) participants had progressed or died in the daratumumab group versus 68 (44%) participants in the control group. In the CASTOR trial, median progression-free survival was 18.0 months in the daratumumab group and 7.3 months in the control group. The number of participants surviving without progression was not reported after a median follow-up of 42.0 months. In the LEPUS trial, median progression-free survival was not reached in either group. The number of participants surviving without progression was not reported after a median follow-up of 8.2 months in the daratumumab group and 6.3 months in the control group. In the POLLUX trial, median progression-free survival was reached after 44.5 months in the daratumumab group and after 17.5 months in the control group. The number of participants surviving without progression was not reported at a median follow-up of 44.3 months.

There was low-certainty evidence that treatment with daratumumab may increase progression-free survival compared with control (HR 0.40, 95% CI 0.29 to 0.56). The magnitude of clinical benefit was graded as 3 out of 4 (progression-free survival benefit compared with comparator HR < 0.65 and estimated progression-free survival gain > 3 months).

Quality of life was assessed in two trials (CASTOR, POLLUX; 1067 participants) with the EORTC QLQ-C30. An increase in the global health status from baseline by at least 10 points was reported for 47.7% of participants in the daratumumab groups and 44.5% of participants in the control groups. There was low-certainty evidence that more participants receiving daratumumab may gain at least 10 points of global health status at 9 months after start of treatment

compared with participants receiving control treatment (RR 1.07, 95% CI 1.07 to 1.22). A decrease of at least 10 points was reported for 51.4% of participants in the daratumumab groups and 52.3% of participants in the control groups. Low-certainty evidence suggests that impairment of at least 10 points of global health status at 9 months after start of treatment is probably similar for participants in both groups (RR 0.98, 95% CI 0.88 to 1.10).

Summary of evidence: harms (from the application)

Transplant-ineligible newly diagnosed multiple myeloma

The ALCYONE and MAIA trials reported adverse events for 1429 participants (*8*, *9*).

Common Terminology Criteria for Adverse Events grade ≥ 3 adverse events were seen in 86% of participants in the daratumumab groups and in 82% of participants in the control groups. There was high-certainty evidence that treatment with daratumumab results in a slight increase in adverse events of grade ≥ 3 compared with controls (RR 1.05, 95% CI 1.0 to 1.11). Serious adverse events were observed in 56% of participants in the daratumumab groups and in 51% of participants in the control groups. There was very-low-certainty evidence that treatment with daratumumab may increase serious adverse events compared with control treatment (RR 1.14, 95% CI 0.86 to 1.51). Both studies also reported on infections and parasitic diseases. These were observed in 30% of participants in the daratumumab groups and in 21% of participants in the control groups. There was high-certainty evidence that treatment with daratumumab increases infections and parasitic diseases compared with controls (RR 1.42, 95% CI 1.19 to 1.70). In addition, pneumonia was observed in 14% and 7% of participants in the daratumumab and control groups, respectively. There was moderate-certainty evidence that treatment with daratumumab probably increases pneumonia compared with control (RR 2.16, 95% CI 1.15 to 4.06).

Transplant-eligible newly diagnosed multiple myeloma

The CASSIOPEIA trial reported adverse events of grade ≥ 3 for 1429 participants (*10*).

Grade ≥ 3 adverse events were observed in 81% of participants in the daratumumab group and in 76% of participants in the control group. There was high-certainty evidence that treatment with daratumumab results in a slight increase in adverse events of grade ≥ 3 compared with controls (RR 1.06, 95% CI 1.0 to 1.13).

Both the CASSIOPEIA and GRIFFIN trials reported serious adverse events, infections and parasitic diseases and pneumonia for 1275 participants (*10*, *11*). Serious adverse events were observed in 46% of participants in the

daratumumab groups and in 48% of participants in the control groups. There was low-certainty evidence that participants treated with daratumumab may experience fewer serious adverse events compared with participants on control treatment (RR 0.94, 95% CI 0.73 to 1.14). Infections and parasitic diseases were observed in 22% of participants in the daratumumab groups and in 20% of participants in the control groups. There was moderate-certainty evidence that treatment with daratumumab probably increases infections and parasitic diseases compared with controls (RR 1.12, 95% CI 0.90 to 1.39). In addition, pneumonia was observed in about 4% of participants in both treatment groups. There was moderate-certainty evidence that treatment with daratumumab may result in little to no difference in pneumonia compared with control treatment (RR 1.05, 95% CI 0.60 to 1.84).

Relapsed or refractory multiple myeloma

The CASTOR and POLLUX studies reported adverse events of grade ≥ 3 for 1429 participants (*13*, *15*). Grade ≥ 3 adverse events were observed in 81% of participants in the daratumumab groups and 70% of participants in the control groups. There was moderate-certainty evidence that treatment with daratumumab results in a slight increase in adverse events of grade ≥ 3 compared with control treatment (RR 1.17, 95% CI 1.04 to 1.31).

The CANDOR, CASTOR, LEPUS and POLLUX studies reported serious adverse events for 1713 participants (*12*–*15*). Serious adverse events were observed in 49% of participants in the daratumumab groups and in 40% of participants in the control groups. There was moderate-certainty evidence that daratumumab may increase serious adverse events compared with control (RR 1.21, 95% CI 1.09 to 1.35).

Data on infections were reported heterogeneously across the trials and were not pooled. The CANDOR and POLLUX trials reported on upper respiratory tract infections. In the CANDOR trial, events for grade 3 and 4 adverse events were reported separately. In the daratumumab group, seven (2%) grade 3 adverse events and one (< 1%) grade 4 upper respiratory tract infections occurred compared with two grade 3 (1%) and no grade 4 events in the control group. In the POLLUX trial, three grade 3 or 4 (1%) upper respiratory tract infections occurred in the daratumumab and in the control group. Grade 3 or 4 treatment emergent events of upper respiratory tract infections were reported in the CASTOR trial (six (3%) in the daratumumab group versus one (0.4%) in the control group) and in the LEPUS trial (20 (14%) in the daratumumab group versus three (4%) in the control group).

The CASTOR and POLLUX studies reported data on pneumonia for 1044 participants. Pneumonia was observed in 13% of participants in the daratumumab groups and 10% of participants in the control groups. There

was low-certainty evidence that treatment with daratumumab may increase pneumonia compared with controls (RR 1.28, 95% CI 0.86 to 1.90).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of multiple myeloma are not available.

Costs/cost–effectiveness

The application presented the findings of a scoping review that identified two cost analyses (*16*, *17*), two health technology assessments (*18*, *19*) and four cost–effectiveness studies (*20–23*) of daratumumab as monotherapy or in combination with bortezomib or lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. Characteristics of the included studies and health technology assessments varied widely, especially regarding patient population (prior lines of therapy ranged from one to a median of five) and time horizon (3 years to life-time horizon).

Cost analyses reported average costs per patient per year in excess of US$ 165 000, with drug acquisitions costs the main driver. Cost–effectiveness analyses reported incremental cost–effectiveness ratios versus different comparators ranging from US$ 30 000 to over US$ 1 million per quality adjusted life year.

Availability

Daratumumab has regulatory approval in many countries including Australia, Canada, Europe, Japan and the United States for use as monotherapy, or in combination with other medicines, for treatment of newly diagnosed or relapsed/refractory multiple myeloma. It has primary patent protection until 2036.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of daratumumab on the EML for treatment of multiple myeloma at this time. The Working Group considered that use of daratumumab would be of greatest value for treatment of patients with newly diagnosed multiple myeloma who are not eligible for transplant. However, the Working Group noted that mature, long-term overall survival data for daratumumab are not yet available in any of the three treatment settings proposed. The Working Group also noted the increased toxicity and high costs associated with daratumumab treatment and toxicity management.

The Committee noted the report of the Medicines Patent Pool that highlighted how the times from starting negotiations to close of agreement

for voluntary licences and from licence to access can be long. Typically, it has taken generic manufacturers 3 to 4 years to develop a generic version of a new medicine and obtain approval from a regulatory authority or from WHO Prequalification. This time can be even longer for biological medicines, which require more lengthy and costly development and manufacturing processes. In addition, patents on the active ingredient, the formulations, the manufacturing processes and trade secrets are particularly important with biotherapeutic medicines. With few exceptions, the current regulatory pathways for approval of biosimilars by regulatory agencies are longer and considerably more costly than those for small molecule generics.

Committee recommendations

The Expert Committee acknowledged that daratumumab was associated with a clinically important survival benefit for patients with multiple myeloma, based on the results reported in the Cochrane systematic review presented in the application. Furthermore, the Committee noted that benefits of daratumumab are observed consistently across all patient subgroups – transplant-eligible newly diagnosed, transplant-ineligible newly diagnose, and relapsed/refractory multiple myeloma. The Committee also noted that the addition of daratumumab to conventional therapy was associated with a modest increase in toxicity.

However, the Committee expressed reservations about the maturity of data on overall survival as the follow-up of the main studies is still ongoing. For most trials, follow-up was less than 3 years. The Committee considered that longer follow-up is required to determine the actual magnitude of benefit and its durability. The Committee considered that understanding the full magnitude of benefit (and harms) is required for new cancer medicines in order for recommendations to be made for inclusion of cancer medicines on the Model List, especially in situations where the price is extremely high, where cure is unlikely and where existing alternatives are listed, as is the case for daratumumab.

The Committee noted that daratumumab is prohibitively expensive and has not been found to be cost-effective, even in high-income countries. The Committee expressed concern about the potential effect of this medicine on budgets, which would be used as part of regimens that include other expensive essential medicines recommended in 2019, namely bortezomib and lenalidomide. The Committee considered that it would be helpful to collect information on access to and availability of bortezomib and lenalidomide for multiple myeloma to explore the effect of EML-listing on access to these cancer regimens in countries with different resources and health system capacity.

While acknowledging the quality of the application in presenting evidence that demonstrates a major clinical benefit from daratumumab, the

Committee nevertheless did not recommend inclusion of daratumumab on the EML at this time because of some uncertainty in the estimates of benefit due to immaturity of the trial data. The Committee requested that an application with updated survival data be submitted for consideration by the Expert Committee in 2023.

Without committing a future Expert Committee to a favourable recommendation to include daratumumab on the EML, the Committee recommended that daratumumab be flagged to the Medicines Patent Pool as a candidate for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this medicine in low- and middle-income countries. In addition, the Committee noted that WHO prequalification processes for monoclonal antibodies for cancer have resulted in prequalification of two molecules – rituximab and trastuzumab. The Committee considered that daratumumab would be a strong candidate for WHO prequalification to facilitate access to affordable and quality-assured products in the event it is listed as an essential medicine. The Committee considered that WHO prequalification and voluntary licence agreements are key actions that could facilitate the current regulatory pathways for approval of daratumumab, either originator or biosimilar, at the country level.

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Tislelizumab – addition for Hodgkin lymphoma – EML

Tislelizumab **ATC Code: L01FF09**

Proposal

Addition of tislelizumab to the complementary list of the EML for the treatment of adults with relapsed or refractory classical Hodgkin lymphoma after at least one second-line chemotherapy.

Applicant

BeiGene Co. Ltd, Beijing, China

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases which advised that, in line with the findings from the EML Cancer Medicines Working Group, there were insufficient mature data on the efficacy and safety of tislelizumab for it to be included in the EML at this time.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strength(s)

Injection: 100 mg/10 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Tislelizumab has not previously been considered for inclusion on the Model List.

Medicines for the treatment of Hodgkin lymphoma in both adults and children were comprehensively reviewed by the Expert Committee in 2015 (*1*). Medicines currently included on the Model Lists as part of treatment protocols for Hodgkin lymphoma are bleomycin, cyclophosphamide, dacarbazine, doxorubicin, etoposide, prednisolone, procarbazine, vinblastine and vincristine.

Public health relevance (burden of disease)

Hodgkin lymphoma is a lymphoid malignancy of B-cell origin most often affecting young adults between the ages of 20 and 40 years. Classical Hodgkin lymphoma accounts for about 95% of all cases (*2*). According to GLOBOCAN, the number of new cases of Hodgkin lymphoma worldwide in 2020 was about 83 000, with an estimated 23 000 deaths. The estimated age-standardized incidence and mortality rates worldwide were 0.98 and 0.26 per 100 000 persons, respectively (*3*).

The prognosis of classical Hodgkin lymphoma is strongly influenced by histological subtype and clinical stage. The lymphocyte-dominated form of the disease has the best prognosis, with a 5-year survival rate of 94%. The lymphocyte-depleted form, however, has a 5-year survival rate of only 27%. With regard to clinical stages, the 5-year survival rate is about 93% for stage I, 86% for stage II, 70% for stage III and 32% for stage IV. Patients with Hodgkin lymphoma have a high cure rate with traditional chemotherapy and radiotherapy. However, about 10–30% of patients have refractory disease following first-line chemotherapy or will experience relapse (*4*–*7*). Following autologous stem cell transplantation, patients have a risk of relapse of nearly 50% (*8*). The prognosis for patients who relapse or progress after autologous stem cell transplantation is extremely poor, with a reported median overall survival of 10.5–27.6 months (*9*, *10*).

Treatment of relapsed/refractory Hodgkin lymphoma is complex and rapidly evolving. Hodgkin lymphoma cells (Reed–Sternberg cells) express high levels of PD-L1 and inhibition of PD-1 through immune checkpoint inhibitors is increasingly studied as treatment for Hodgkin lymphoma.

Summary of evidence: benefits (from the application)

The application presented the results of study BGB-A317-203, an open-label, single-arm, multicentre phase II trial in China that evaluated the efficacy and safety of tislelizumab in 70 participants with relapsed/refractory classical Hodgkin lymphoma (*11*).

After median follow-up of 9.8 months, 61 (87.1%) participants achieved an objective response, with 44 (62.9%) participants achieving a complete response and 17 (24.3%) participants achieving a partial response.

Of the 13 participants who had previously undergone autologous stem cell transplantation, 12 (92.3%) achieved an objective response, with nine (69.2%) achieving a complete response. All four participants who had previously received the antibody-drug conjugate brentuximab vedotin achieved a complete response.

Of the 25 participants with primary refractory disease, 20 (80%) achieved an objective response, including 13 (52%) who achieved a complete response. The median time to response was 12 weeks (range 8.9 to 42.1 weeks).

After a median follow-up of 9.6 months, the median progression-free survival had not been reached. At 9 months, the progression-free survival rate

was 74.5% (95% confidence interval (CI) 70.5% to 89.4%). After a median follow-up from the first response of 6.7 months, the median duration of response had not been reached for the 61 participants who achieved a response. One patient had died by the data cut-off date due to disease progression. The 9-month overall survival rate was 98.6%.

Direct comparative data of tislelizumab with other PD-1 monoclonal antibodies or other treatments such as brentuximab vedotin for relapsed/refractory classical Hodgkin lymphoma are lacking. The application presented indirect comparisons of efficacy reported for tislelizumab (*11*), sintilimab (*12*), camrelizumab (*13*), pembrolizumab (*14*, *15*) and nivolumab (*16–20*). Objective response rates were 87.1% for tislelizumab, 80.4% for sintilimab, 76.0% for camrelizumab, 71.9% for pembrolizumab and 71.2% for nivolumab. The complete response rate for tislelizumab was 62.9%, while for sintilimab, camrelizumab, pembrolizumab and nivolumab they were 33.7%, 28.0%, 27.6% and 21.0%, respectively.

Summary of evidence: harms (from the application)

The safety results of trial BGB-A317-203 were presented in the application (*11*). In this study, 65/70 (92.9%) of participants experienced adverse events, most of which were grade 1 or 2. Grade 3 or above adverse events occurred in 15/70 (21.4%) of participants including two participants with grade 4 events (increased serum creatinine phosphokinase and thrombocytopenia). No grade 5 adverse events were reported. The most common adverse events were fever (54.3%), hypothyroidism (32.9%), weight gain (30.0%), upper respiratory infection (30.0%), leukopenia (18.6%), cough (17.1%) and pruritus (17.1%). The most common adverse events of grade 3 and above were upper respiratory tract infection and pneumonia.

Overall, safety information of tislelizumab comes from BGB-A317-203, and two additional single-agent clinical studies of tislelizumab in solid tumours – BGB-A317-001 (*21*) and BGB-A317-102 (*22*) involving 821 participants in total. Across the three trials, the median administration time of tislelizumab was 16 weeks (range 0.6 to 162 weeks). Up to 35.7% of participants received tislelizumab treatment for at least 6 months and 20.0% received tislelizumab treatment for at least 12 months. The incidence of adverse events of all grades was 71.0% among the 821 participants treated with tislelizumab. Adverse events with an incidence greater than or equal to 10% included fatigue, rash, hypothyroidism, increased alanine aminotransferase and increased aspartate aminotransferase.

Since tislelizumab has only completed a single-arm phase II clinical trial and the phase III clinical trial comparing tislelizumab with other products is still in progress, no comparative safety data for tislelizumab versus other PD-1 monoclonal antibodies are available.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of Hodgkin lymphoma are not available.

Costs/cost–effectiveness

No cost–effectiveness analysis data were presented in the application.

Tislelizumab is priced at ¥ 10 688 per 100 mg vial. The administered dose used in the phase II trial was 200 mg every 3 weeks.

The China Primary Health Care Foundation, in conjunction with BeiGene, initiated the Patient assistance programme "Wei Ni, Qian Fang Bai Ji". This programme reduces the cost of first-time medication and the cost for patients who need long-term medication. Patients only need to pay for five cycles of treatment and get 1-year medical treatment. The annual treatment cost for patients for tislelizumab under the patient assistance programme is about ¥ 106 900. The annual treatment cost for other PD-1 antibodies for classical Hodgkin lymphoma in China under the patient assistance programme are reported as ¥ 99 000 for sintilimab and ¥ 119 000 for camrelizumab.

Availability

Tislelizumab received regulatory approval from the National Medical Products Administration of the People's Republic of China in December 2019 for the treatment of relapsed/refractory classical Hodgkin lymphoma after at least one second-line chemotherapy.

Tislelizumab had not been approved for marketing and use by other national regulatory agencies at the time of consideration by the Expert Committee.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of tislelizumab on the EML for treatment of relapsed/refractory Hodgkin lymphoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and with short follow-up), its high price and unknown cost–effectiveness.

Committee recommendations

The Expert Committee acknowledged that Hodgkin lymphoma is a serious disease with a high incidence rate and costly treatment and follow-up. The Committee noted that the disease has a relatively high 5-year survival rate with conventional chemotherapy and radiotherapy. However, for patients with

relapsed or refractory disease, the prognosis is poor and effective treatments are limited.

The Committee considered that the application for inclusion of tislelizumab on the EML for Hodgkin lymphoma was premature. The available data for the efficacy and safety of tislelizumab in patients with Hodgkin lymphoma were limited to one phase II single-arm trial, with a small number of patients. Comparative evidence of efficacy and safety versus other treatments was also lacking. The available data were therefore considered insufficient to evaluate the clinical benefit and safety of tislelizumab as an essential medicine.

The Committee also noted that tislelizumab is currently very expensive, has unknown cost–effectiveness and has very limited global regulatory approval and availability. Therefore, the Committee did not recommend inclusion of tislelizumab on the EML for the treatment of Hodgkin lymphoma.

However, the Committee recognized the potentially important role of immune checkpoint inhibitors as a therapeutic class in the treatment of relapsed/refractory Hodgkin lymphoma. The Committee advised that it would welcome an application with more mature data and including all immune checkpoint inhibitors used in the treatment of Hodgkin lymphoma for consideration for EML listing in the future. The Committee also considered that immune checkpoint inhibitors could be flagged to the Medicines Patent Pool as candidates for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this class of medicines in low- and middle-income countries.

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Tislelizumab – addition for urothelial cancer – EML

Tislelizumab **ATC Code: L01FF09**

Proposal

Addition of tislelizumab to the complementary list of the EML for the treatment of locally advanced or metastatic urothelial carcinoma in patients with high PD-L1 expression who have failed prior platinum-containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) and whose disease has have progressed within 12 months.

Applicant

BeiGene Co., Ltd, Beijing, China

WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases which advised that, in line with the findings from the EML Cancer Medicines Working Group, there were insufficient mature data on the efficacy and safety of tislelizumab. The technical department suggested that tislelizumab for this indication could be reconsidered in the future based on additional evidence and increased understanding of the feasibility of its appropriate use in low-resource settings.

EML/EMLc

EML

Section

8.3.3 Immunomodulators

Dose form(s) & strength(s)

Injection: 100 mg/10 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Tislelizumab has not previously been considered for inclusion on the Model List.

The Model List does not currently include medicines specifically for the treatment of urothelial carcinoma in any line of therapy.

Public health relevance (burden of disease)

Urothelial carcinoma refers to tumours in the epithelial structure from the kidney's exit to the urethra. About 90–95% of urothelial carcinoma tumours originate from the bladder, with the remainder from the ureter, renal pelvis and proximal urethra (*1*). In 2020, bladder cancer ranked as the 11th most common tumour worldwide and 14th for mortality (*2*). According to GLOBOCAN, there were about 570 000 new cases of bladder cancer in 2020 and an estimated 212 000 deaths. The global age-standardized incidence and mortality rates were 5.6 and 1.9 per 100 000 persons, respectively *(2)*.

The survival rate of bladder cancer patients decreases with disease progression and relapse tends to occur early (*3*). Patients with distant metastases have a poor prognosis due to the inability to remove the tumour surgically and lack of effective treatments. In these patients the 5-year relative survival rate is about 5% (*4*).

For the past 30 years, cisplatin-based combination chemotherapy has been the standard treatment for locally advanced/metastatic urothelial carcinoma. Classical therapies include: gemcitabine and cisplatin; methotrexate, vinblastine, doxorubicin and cisplatin; and dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (*5*,*6*). The overall response rate to these treatments is about 40–50% and the median overall survival is about 14–15 months. However, about 40–50% of patients with metastatic urothelial carcinoma cannot tolerate cisplatin treatment due to their poor physical condition or impaired renal function. These patients can only use carboplatin-based treatment options, which have an overall response rate of about 30–40% with a median overall survival of 9–10 months (*7*, *8*). There is currently no standard second-line treatment for people with locally advanced/metastatic urothelial carcinoma and disease progression after first-line chemotherapy. Paclitaxel, pemetrexed, docetaxel, gemcitabine and doxorubicin are commonly used clinically, but their efficacy is limited with an overall response rate of about 12% and overall survival of 5–7 months (*8*, *9*).

Summary of evidence: benefits (from the application)

The application presented the results of study BGB-A317-204, a single-arm, non-randomized, open-label, multicentre phase II trial conducted in China and South Korea that assessed the efficacy and safety of tislelizumab in 113 participants with locally advanced or metastatic urothelial carcinoma, who had disease progression with platinum-based chemotherapy and who had not received prior PD-(L)1 inhibitor treatment and who had ≥ 25% of

tumour/immune cells expressing PD-L1 (*10*). The primary endpoint was the overall response rate assessed by an independent review committee. After median follow-up of 9.4 months, 20 (18%) participants continued to receive tislelizumab, while the remaining 93 (82%) discontinued treatment. Reasons for discontinuation were disease progression (53 participants), adverse events (19 participants), withdrawn consent (11 participants) and symptomatic deterioration (10 participants). Of 104 patients who could be evaluated, a confirmed objective response was observed in 25 (overall response rate (ORR) 24%, 95% confidence interval (CI) 16% to 33%), including 10 patients with complete response and 15 with partial response as assessed by the independent review committee. Median progression-free survival and overall survival were 2.1 months (95% CI 2.0 to 3.2 months) and 9.8 months (95% CI 7.5 to 12.5 months), respectively.

Direct comparative data of tislelizumab with other PD-1 monoclonal antibodies for urothelial carcinoma are lacking. The application presented indirect comparisons of efficacy reported for tislelizumab (*10*), atezolizumab (*11*, *12*), durvalumab (*13*), avelumab (*14*), nivolumab (*15*) and pembrolizumab (*16*, *17*). Objective response rates (among PD-L1 positive patients, defined differently across the studies) were 24% for tislelizumab, 23–26% for atezolizumab, 28% for durvalumab, 24% for avelumab, 28% for nivolumab and 20–30% for pembrolizumab.

Summary of evidence: harms (from the application)

Safety results from study BGB-A317-204 were presented in the application (*10*). In this study, 106 (94%) participants experienced at least one adverse effect considered to be related to tislelizumab by the investigator. The most common treatment-related adverse events were anaemia (27%) and pyrexia (20%). Most treatment-related adverse events were grade 1–2 in severity. Anaemia (7%) and hyponatraemia (5%) were the only grade 3 or 4 events occurring in ≥ 5% of participants. Treatment-related adverse events led to treatment discontinuation in 14% of participants. Serious treatment-related adverse events occurred in 37% of participants, the most common being pyrexia (4%), and upper respiratory tract infection, urinary tract infection and drug eruption (3% each). Among seven participants with a treatment-related adverse event leading to death, three were considered possibly related to the study treatment by the investigators (hepatic failure, two participants; respiratory arrest, one patient).

In the study, 27% of participants experienced immune-related adverse events; events affecting ≥ 5% of participants included skin adverse reactions (12%), hypothyroidism (11%) and hyperthyroidism (6%). Eight (7%) participants had immune-related adverse events of grade ≥ 3; no fatal immune-related adverse events were reported.

Overall, safety information of tislelizumab comes from two single-agent clinical studies of the use of tislelizumab in solid tumours (*18*, 19) and a single-agent study of tislelizumab in Hodgkin lymphoma (*20*), involving a total of 821 participants. The tumour types of the participants included in these studies varied and included 39 participants with urothelial carcinoma. Participants received tislelizumab at a dose of either 200 mg or 5 mg/kg every 3 weeks. The median administration time of tislelizumab was 16 weeks (range 0.6–162 weeks). Tislelizumab treatment continued for at least 6 months in 35.7% of participants, while 20.0% of participants received tislelizumab treatment at least 12 months. The incidence of adverse events of all grades was 71.0% among the 821 participants treated with tislelizumab. Adverse events with an incidence ≥ 10% included fatigue, rash, hypothyroidism, increased alanine aminotransferase and increased aspartate aminotransferase.

Since tislelizumab has only completed a single-arm phase II clinical trial, and the phase III clinical trial comparing tislelizumab with other products is still in progress, no comparative safety data with other PD-1 monoclonal antibodies are available.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of urothelial carcinoma are not available.

Costs/cost–effectiveness

No cost–effectiveness analysis data for tislelizumab were presented in the application.

Tislelizumab is priced at ¥ 10 688 per vial. The administered dose used in the phase II trial was 200 mg every 3 weeks.

Vial prices for alternative anti-PD1 monoclonal antibodies presented in the application were US$ 6495 for nivolumab (240 mg/24 mL), US$ 3671 for durvalumab (500 mg/10 mL) and US$ 4800 for pembrolizumab (100 mg/4 mL).

The China Primary Health Care Foundation, in conjunction with BeiGene, initiated the Patient Assistance Programme "Wei Ni, Qian Fang Bai Ji". This programme reduces the cost of first-time medication and the cost for patients who need long-term medication. Patients only need to pay for five cycles of treatment and get 1 year of medical treatment. The minimum annual treatment cost is about ¥ 106 900.

Availability

Tislelizumab received regulatory approval from the National Medical Products Administration of the People's Republic of China in April 2020 for the treatment

of patients with locally advanced or metastatic urothelial carcinoma with high PD-L1 expression, who have failed prior platinum-containing chemotherapy and whose disease has progressed within 12 months.

Tislelizumab was not approved for marketing and use by other national regulatory agencies at the time of EML consideration.

Other considerations

Tislelizumab has not yet been scored on the European Society for Medical Oncology's magnitude of clinical benefit scale for this indication (*21*).

The application was reviewed by the EML Cancer Medicines Working Group. The Working Group advised that it did not support the inclusion of tislelizumab on the EML for treatment of urothelial carcinoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and with short follow-up), the cost of tislelizumab is high and its cost–effectiveness is not known for this indication.

Committee recommendations

The Expert Committee noted that bladder cancer is a common malignancy worldwide and accounts for the vast majority of cases of urothelial carcinoma. The Committee noted that the EML currently includes the medicines in the cisplatin-based chemotherapy protocols that are considered the standard of care for first-line treatment of locally advanced and metastatic urothelial carcinoma. However, evidence for their use in the treatment of urothelial cancer has not been specifically reviewed.

The Committee considered that the application for inclusion of tislelizumab on the EML for locally advanced or metastatic urothelial cancer was premature. The available data for the efficacy and safety of tislelizumab in patients with urothelial carcinoma were limited to one single-arm, non-randomized, open-label phase II study. Comparative evidence of efficacy and safety versus other treatments was also lacking. The available data were therefore considered insufficient to evaluate the benefits and harms of tislelizumab for listing as an essential medicine.

The Committee also noted that tislelizumab is expensive, its cost–effectiveness is not known, and it has very limited global regulatory approval and availability. Therefore, the Committee did not recommend inclusion of tislelizumab on the EML as a second-line treatment for locally advanced or metastatic urothelial carcinoma.

However, the Committee recognized the potentially important role of immune checkpoint inhibitors, as a therapeutic class, in the treatment of platinum-refractory urothelial cancer. The Committee advised that it would welcome an application, with more mature data, and including all immune checkpoint inhibitors used in the treatment of urothelial cancer, for

consideration for EML listing in the future. The Committee also considered that immune checkpoint inhibitors could be flagged to the Medicines Patent Pool as candidates for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this class of medicines in low- and middle-income countries.

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8.2.4 Hormones and antihormones

Enzalutamide – addition – EML

Enzalutamide **ATC Code: L02BB04**

Proposal

Addition of enzalutamide to the EML for the treatment of metastatic castration-resistant prostate cancer.

Applicant

Knowledge Ecology International (KEI)

WHO technical department

Noncommunicable Diseases

EML/EMLc

EML

Section

8.2.4 Hormones and antihormones

Dose form(s) & strength(s)

Capsule: 40 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

In 2017, the Committee considered an application requesting the inclusion of enzalutamide on the EML for the treatment of metastatic castration-resistant prostate cancer, but did not recommend inclusion. Instead, the Committee recommended a comprehensive review of prostate cancer medicines, including abiraterone, be considered at its meeting in 2019 (*1*).

In 2019, following consideration of an application proposing the addition of abiraterone and enzalutamide to the EML for treatment of metastatic castration-resistant prostate cancer, the Committee recommended the addition of abiraterone, but not enzalutamide (*2*). The Committee noted that abiraterone

and enzalutamide had been shown to be effective treatments for metastatic castration-resistant prostate cancer, both in chemotherapy-naïve and pretreated patients. The Committee noted that abiraterone had not shown any relevant clinical advantage over enzalutamide in terms of efficacy outcomes or safety. However, the Committee recognized the potential advantages offered by abiraterone in terms of: emerging dosing strategies (lower doses may be possible when administered with food); reduced pill burden potentially improving adherence; wider availability of generics; and potential associated cost savings.

Given that metastatic prostate cancer often requires treatment over longer periods (i.e. more than 1 year) and that low dosing and availability of generics would be associated with substantial cost savings, the Committee did not to recommend listing enzalutamide as an alternative to abiraterone under a square box listing. While enzalutamide is an effective therapeutic option for metastatic castration-resistant prostate cancer, its use instead of abiraterone could result in considerable additional expenditure at the country level, without additional clinical benefit. The Committee considered that the addition of abiraterone alone to the EML serves to support its use, promoting competition between brand and generic medicines, and improving access and affordability.

Public health relevance (burden of disease)

Prostate cancer is the second most common cancer in men and the fourth most common cancer overall. In 2018, about 1.3 million men were diagnosed with prostate cancer worldwide (*3*).

With early treatment, and if tumours are localized, the prognosis for prostate cancer patients is often favourable. However, some patients will relapse despite androgen deprivation therapy (so-called castration), which leads to castration-resistant prostate cancer when the disease is no longer responsive to androgen deprivation therapy, thus limiting the available treatment options. Access to second-generation therapies such as enzalutamide therefore becomes critical to extending patients' lives and allowing them to have an improved quality of life.

Six treatments are currently used to treat castration-resistant prostate cancer. Enzalutamide and abiraterone acetate are the only orally administered therapies. Other treatments are invasive and require intravenous administration, leukapheresis or the use of radiopharmaceuticals.

Summary of evidence: benefits (from the application)

Enzalutamide in metastatic castration-resistant prostate cancer

The application presented the same data from the AFFIRM and PREVAIL trials that were presented in the 2019 application.

The AFFIRM trial was a phase III, randomized, double-blind, placebo-controlled, multicentre trial to study the efficacy and safety of enzalutamide in participants with metastatic castration-resistant prostate cancer who had previously taken docetaxel (*4*). A total of 1199 adult males, aged 41 to 92 years, were randomized in a 2:1 ratio, where 800 participants received a dose of 160 mg of enzalutamide once a day, 399 participants received a placebo, and all continued on androgen deprivation therapy. Overall survival was 18.4 months for the enzalutamide arm versus 13.6 months for the placebo arm (hazard ratio (HR) for death 0.63, 95% confidence intervals (CI) 0.53 to 0.75; $P < 0.001$). Progression-free survival was 8.3 months for enzalutamide versus 2.9 months for placebo (HR 0.40, 95% CI 0.35 to 0.47; $P < 0.001$).

The PREVAIL trial was a phase III, randomized, double-blind, placebo-controlled clinical trial that investigated enzalutamide as the first-line therapy in 1717 participants with metastatic castration-resistant prostate cancer (*5*). The study was halted after interim analysis results showed benefit for enzalutamide. Significantly fewer deaths were reported in the enzalutamide arm compared with the placebo arm (28% versus 35%; HR 0.71, 95% CI 0.60 to 0.84; $P < 0.001$).

Comparisons of enzalutamide and abiraterone acetate in metastatic castration-resistant prostate cancer

Two separate meta-analyses pooled data from eight randomized trials of novel drugs that target the androgen receptor pathway (enzalutamide, abiraterone and orteronel) in participants with metastatic castration-resistant prostate cancer (*6*, *7*). The meta-analyses included the AFFIRM and PREVAIL trials, and two trials of enzalutamide versus bicalutamide (TERRAIN and STRIVE). Only AFFIRM and PREVAIL reported overall survival. Since the heterogeneity between the clinical trials was high, a random-effects model was used to calculate HRs for overall survival and progression-free survival. Pooled HRs for overall survival were similarly significant for enzalutamide (HR 0.71, 95% credible interval (CrI) 0.54 to 0.89) and abiraterone (HR 0.78, 95% CrI 0.61 to 0.98). Pooled HRs for progression-free survival favoured enzalutamide (HR 0.36, 95% CrI 0.21 to 0.59) over abiraterone (HR 0.59, 95% CrI 0.35 to 1.00) (*7*).

A retrospective analysis of 2591 and 807 patients with metastatic castration-resistant prostate cancer who started treatment with abiraterone and enzalutamide, respectively, concluded that patients on abiraterone acetate therapy had higher medication adherence and lower risk for dose reduction than those on enzalutamide therapy (*8*). The authors proposed that improved medication adherence may be associated with longer duration of treatment and better survival. A separate analysis of the same patient population compared the duration of treatment in patients started on abiraterone and enzalutamide (*9*). At 3 months, patients on abiraterone had fewer discontinuations of metastatic

castration-resistant prostate cancer treatments (HR 0.73, 95% CI 0.59 to 0.91; $P = 0.004$) or of any prostate cancer treatment (HR 0.61, 95% CI 0.45 to 0.83; $P = 0.002$) compared with patients on enzalutamide. The median duration of metastatic castration-resistant prostate cancer treatments was 4.1 months longer for patients on abiraterone than those on enzalutamide (18.3 versus 14.2 months; $P < 0.001$). The authors suggested that patients started on abiraterone acetate, compared with those started on enzalutamide, had a longer combined duration of metastatic castration-resistant prostate cancer or prostate cancer treatments. Both of these studies were funded by Janssen Scientific Affairs, the manufacturer of abiraterone.

A 2019 phase II, randomized, open-label, crossover trial investigated the optimal sequencing of enzalutamide and abiraterone plus prednisone in participants with metastatic castration-resistant prostate cancer (*10*). Participants were randomized to receive abiraterone acetate 1000 mg orally once daily + prednisone 5 mg orally twice daily until prostate-specific antigen (PSA) progression followed by crossover to enzalutamide 160 mg orally once daily (group A, 101 participants) or the opposite sequence (group B, 101 participants). Enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor based on time to second PSA progression. In contrast, abiraterone acetate did not. Median time to second PSA progression was longer in group A than group B (19.3 months versus 15.2 months; HR 0.66, 95% CI 0.45 to 0.97; $P = 0.036$) at a median follow-up of 22.8 months (interquartile range 10.3–33.4). PSA responses to second-line therapy were seen in 36% of participants for enzalutamide and 4% of participants for abiraterone.

The application also presented a summary of evidence for enzalutamide in non-metastatic castration-resistant prostate cancer and in hormone-sensitive metastatic prostate cancer.

Enzalutamide in non-metastatic castration-resistant prostate cancer

The PROSPER trial was a phase III, randomized, double-blind, placebo-controlled trial of enzalutamide plus androgen deprivation therapy in 1401 participants with non-metastatic castration-resistant prostate cancer and with a rapidly rising PSA level (*11*). Enzalutamide treatment was associated with a 71% lower risk of metastasis or death compared with placebo. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (HR 0.29, 95% CI 0.24 to 0.35; $P < 0.001$). The time to the first use of subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 months versus 17.7 months; HR 0.21, 95% CI 0.17 to 0.26; $P < 0.001$) with subsequent antineoplastic therapy used in 15% of participants in the enzalutamide group and 48% of participants in the placebo group.

The final analysis of overall survival in the PROSPER trial (October 2019) showed that treatment with enzalutamide was associated with a 27% lower risk of death than placebo (*12*). Median overall survival was 67 months (95% CI 64.0 months to not reached) in the enzalutamide arm and 56.3 months (95% CI 54.4 to 63.0 months) in the placebo arm (HR 0.73, 95% CI 0.61 to 0.89; $P = 0.001$).

Summary of evidence: harms (from the application)

The different studies that analysed the efficacy of enzalutamide also reported adverse effects associated with it.

In the AFFIRM trial, the incidence of grade 3 or higher adverse events was lower in the enzalutamide arm compared with the placebo arm (45.3% versus 53.1%) (*4*). Grade 3 or higher fatigue, diarrhoea, musculoskeletal pain, headache and seizures occurred slightly more frequently in participants treated with enzalutamide. Adverse events causing death occurred in 3% and 4% of participants treated with enzalutamide and placebo, respectively.

In the PREVAIL trial, grade 3 or higher adverse events were reported in 43% of participants in the enzalutamide arm compared with 37% of participants in the placebo arm (*5*). The most commonly reported adverse events occurring at least 2% more frequently in the enzalutamide arm were fatigue, back pain, constipation and arthralgia. The most commonly reported adverse event of grade 3 or higher in the enzalutamide arm was hypertension, which occurred in 7% of participants.

In the PROPSER trial, adverse events of grade 3 or higher occurred in 31% of participants receiving enzalutamide compared with 23% of participants receiving placebo (*11*).

The most common grade 3–4 adverse events reported in the crossover trial (*10*) were hypertension (27% in group A versus 18% in group B) and fatigue (10% in group A versus 4% in group B). Serious adverse events were reported in 15% of participants in group A and 20% of participants in group B. No treatment-related deaths occurred.

The meta-analysis by Kang et al. found that the risk of adverse events did not differ between enzalutamide and control arms (*7*).

If grade 3 or higher adverse events occur, or if the patient develops toxicity, enzalutamide should be stopped for 1 week or until symptoms subside to grade 2 or less. Of note, enzalutamide strongly interacts with medicines that inhibit CYP2C8; therefore if co-administration cannot be avoided, the dose of enzalutamide should be reduced to 80 mg once daily for as long as the drug continues to be effective and tolerated.

Additional evidence (not in the application)

Low-dose abiraterone dosing

A 2018 prospective phase II, randomized, non-inferiority trial investigated the activity of low-dose abiraterone (250 mg/day) administered with a low-fat meal compared with standard dose abiraterone (1000 mg/day) administered under fasting conditions in 72 patients with metastatic castration-resistant prostate cancer (*13*). The primary endpoint was log change in PSA, as a pharmacodynamic biomarker for efficacy. Secondary endpoints included progression-free survival, PSA response (≥ 50% reduction), change in androgen levels and pharmacokinetics. Low-dose abiraterone was found to be non-inferior to standard-dose abiraterone, according to the predefined non-inferiority criteria. Mean log change in PSA was –1.59 and –1.19 in the low- and standard-dose arms, respectively. PSA response and progression-free survival did not differ between the treatment arms. The decrease in androgen levels was similar in both treatment arms. On the basis of this trial, the low-dose abiraterone with food regimen has been included in the guidelines of the National Comprehensive Cancer Network for prostate cancer as an alternative to the standard-dose treatment regimen (*14*).

A survey of 118 medical oncologists in India reported that 93.2% of practitioners believed that the use of low-dose abiraterone would improve compliance and 100% agreed that it would reduce costs of treatment (*15*). Just over half (55%) of respondents were prescribing low-dose abiraterone only in limited-resource settings, 6.8% said they had changed their practice after publication of the above-mentioned trial (*13*) and 28.8% indicated that they would change to low-dose abiraterone prescribing. Only 9.3% of respondents said they would not use low-dose abiraterone. Cost savings to the Indian health care system of changing to low-dose abiraterone were estimated to be US$ 182 million a year (*15*).

WHO guidelines

Not available

Costs/cost–effectiveness

Many of the cost–benefit studies for enzalutamide have used the price of the originator product. Generic enzalutamide is now also available and as the competition among generic suppliers expands, prices should decline considerably.

The application recommends that WHO consider the cost–effectiveness when the drugs are expensive (from the originator) and when the drugs are less expensive (from generic suppliers), and look at reasonable scenarios for generic prices falling over time.

The application describes prices for a 40 mg capsule of enzalutamide in different countries, ranging from as high as US$ 119.18 in the United States of America to as low US$ 2.31 from generic manufacturers in India. In 2016, Canada-based Biolyse Pharma offered to sell generic enzalutamide to the US Medicare programme for US$ 3 for a 40 mg tablet, or US$ 12 for a daily dose of 160 mg. But generic prices could fall much further, given active pharmaceutical ingredient (API) costs. In previous years, before generics were available, some publicly quoted prices for the API enzalutamide were in the range of US$ 6000 to US$ 13 000 per kilogram.

The National Institute for Health and Care Excellence (NICE) of the United Kingdom of Great Britain and Northern Ireland published technology appraisal guidance for enzalutamide as a second-line treatment for metastatic castration-resistant prostate cancer after docetaxel (*16*). It recommends enzalutamide as an option for treating adult patients with hormone-relapsed metastatic prostate cancer only if their disease has progressed during or after docetaxel-containing chemotherapy, they have not had treatment with abiraterone and the manufacturer provides enzalutamide with the discount agreed in the patient access scheme. NICE also considered that enzalutamide should be compared with abiraterone for patients who had received one course of chemotherapy, and with best supportive care for patients who had received two or more chemotherapy courses. For patients who had received one course of chemotherapy, the NICE Appraisal Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an incremental cost–effectiveness ratio (ICER) of £ 22 600 per quality-adjusted life year (QALY) gained for enzalutamide compared with abiraterone. The Committee accepted that this ICER was associated with uncertainty, but it was satisfied that it would remain lower than £ 30 000 per QALY gained on balance. For patients who had received two or more chemotherapy courses, the Committee noted that the ICER estimated by the manufacturer for enzalutamide compared with best supportive care was £ 45 500 per QALY gained and that the ICER estimated by the Evidence Review Group was £ 48 000 per QALY gained. The Committee agreed that enzalutamide would be considered an end-of-life treatment as defined by NICE for this subgroup. The magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of National Health Service resources. The Committee did not see sufficient evidence to make any recommendations on the clinical– and cost–effectiveness of sequential use of enzalutamide and abiraterone.

As in the 2019 application, a summary of numerous studies that investigated the cost–effectiveness of enzalutamide in various settings was presented.

The application anticipates that API costs for enzalutamide will decline over time to between US$ 300 and US$ 900 per kilogram, resulting in daily treatment costs as low as US$ 0.048 to US$ 0.144.

Availability

Originator brand enzalutamide, manufactured by Astellas Pharma, has worldwide regulatory approval. One generic version is available in India.

Other considerations

Based on the results of the AFFIRM study (*4*), enzalutamide received a score of 4 on the European Society of Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 for use as a second-line treatment of metastatic castration-resistant prostate cancer after docetaxel (*17*).

Based on the results of the PREVAIL study (*5*, *18*), enzalutamide received a score of 3 on the ESMO-MCBS v1.1 for use as a first-line treatment of metastatic castration-resistant prostate cancer (*17*).

The EML Cancer Medicines Working Group noted that enzalutamide met the criteria for survival benefit and ESMO-MCBS score to be considered for inclusion in the EML and appeared to demonstrate comparable efficacy and safety to abiraterone, which is currently included on the EML. However, no direct trial data are available.

Consideration was given to what the added benefit of including enzalutamide on the EML might be, in the absence of any clinical advantage over abiraterone. There is currently no evidence that having both agents available would result in improved access or cost benefits in terms of market competition. However, having options available may provide opportunities for countries to negotiate better prices as part of their national procurement processes. Nevertheless, the Working Group concluded that in view of financial concerns it did not support inclusion of enzalutamide on the EML.

The Working Group also noted the evidence on the use of low-dose abiraterone and considered that this was an area where WHO could advocate for this cost-saving approach to treatment.

Committee recommendations

The Expert Committee noted that prostate cancer is the second most common cancer in men worldwide and the fourth most common cancer overall, and that treatment options for metastatic, castration-resistant prostate cancer are limited. The Committee acknowledged that enzalutamide and abiraterone, as oral treatments, offer several advantages over other treatment options as they do not require intravenous administration, leukapheresis, or the use of radiopharmaceutical compounds.

The Committee recalled its previous recommendations not to include enzalutamide on the EML, recommending instead listing abiraterone based on advantages offered by dosing strategies, lower pill burden, better adherence and availability of generics which would allow potential cost savings. The Committee noted that the current cost of enzalutamide is very high for both patients and health systems.

The Committee noted that enzalutamide for metastatic, castration-resistant prostate cancer largely meets the EML criteria for survival benefit (i.e. at least 4 to 6 months survival gain) and the European Society of Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 score, and appears to demonstrate comparable efficacy and safety to abiraterone. However, no direct trial data are available, leaving some uncertainty about which medicine is the best therapeutic option. Enzalutamide has a different mechanism of action and a different toxicity profile, making it a first-choice medicine in patients not eligible to be treated with or unable to tolerate abiraterone. Unlike abiraterone, enzalutamide does not require concomitant use of prednisolone.

The Committee considered that having multiple treatment options included on the EML may provide opportunities for countries to negotiate better prices as part of their national procurement processes. In some countries, competition and price reduction will be facilitated by the fact both abiraterone and enzalutamide have generic versions available. Therefore, the Committee recommended that enzalutamide be included on the complementary list of the EML as a therapeutic alternative to abiraterone. The listing of abiraterone should be qualified with a square box indicating enzalutamide as an alternative for national selection. The Committee considered that this could provide opportunities for cost savings at the country level and increase access to medicines associated with favourable outcomes. As currently the prices of abiraterone and enzalutamide are a major obstacle for health care systems, the Committee recommends that countries address this problem through multiple actions, including price negotiations, competitive tendering and expanded use of generics.

The Committee recommended that the Medicines Patent Pool explore with manufacturers how to facilitate affordable access to enzalutamide through public health-oriented licences. The Committee also requested that WHO prioritize abiraterone and enzalutamide as potential candidates for prequalification to facilitate access to affordable and quality-assured products.

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Fulvestrant – addition – EML

Fulvestrant **ATC Code: L02BA03**

Proposal

Addition of fulvestrant to the complementary list of the EML for the treatment of metastatic breast cancer.

Applicant

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WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that there is insufficient evidence of significant clinical effect of fulvestrant in comparison to medicines already included in the EML.

EML/EMLc

EML

Section

8.2.4 Hormones and antihormones

Dose form(s) & strength(s)

Injection: 250 mg/5 mL in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Fulvestrant has not previously been considered for inclusion on the EML.

In 2015, as part of a comprehensive review of cancer medicines on the EML, the following medicines were endorsed for inclusion on the EML for use in protocols for the treatment of metastatic breast cancer: capecitabine, cyclophosphamide, docetaxel, doxorubicin, paclitaxel, vinorelbine, anastrozole and tamoxifen. Trastuzumab was also recommended for treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage and metastatic breast cancer (*1*).

Public health relevance (burden of disease)

Breast cancer is the most frequent malignant disease in women. The estimated number of new cases in 2020 was 2 261 419, accounting for 25% of all cancers in women. The global age-standardized incidence rate is 47.8/100 000 people, with the highest rate observed in Australia and New Zealand (95.5/100 000 people). Incidence is much lower in Africa and Asia (< 50/100 000 people). The global age-standardized mortality rate is 13.6 per 100 000, ranging from 9.8 per 100 000 in Eastern Asia to 27.5 per 100 000 in Melanesia (*2*).

Many women initially diagnosed in early stages will progress to a metastatic stage. It has been estimated that only 25% of the women living with metastatic breast cancer are new cases, while 75% being recurrences of previously localized disease (*3*).

While improved early detection and advances in systemic therapy for the early-stage disease have resulted in some decline in breast cancer mortality since 1989, metastatic breast cancer remains largely incurable with a median survival of about 24 months (*4*). Factors associated with poor survival include age ≥ 50 years, visceral disease, shorter disease-free interval, aneuploid tumours, tumours with a high S-phase fraction, p53 accumulation, low BCL-2 expression, negative hormone receptor status, and positive HER2 status (*5*).

Summary of evidence: benefits (from the application)

The applicants conducted a literature search for randomized trials and systematic reviews of fulvestrant plus aromatase inhibitors in women with metastatic breast cancer, and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool, and judgements about precision, consistency, directness and likelihood of publication bias were made following the GRADE approach.

Six systematic reviews (*6–11*) (used to identify relevant studies) and three randomized trials (*12–14*) were identified. Two trials reported data to estimate the effect on overall survival and were included in the meta-analysis (*12*, *13*).

The open-label, phase III FACT trial was conducted in premenopausal women receiving a gonadotropin-releasing hormone agonist and postmenopausal women, both groups with hormone-receptor-positive breast cancer who had relapsed after primary treatment (*12*). A total of 514 participants were randomized 1:1 to receive a loading dose of fulvestrant followed by monthly fulvestrant plus daily anastrozole (n = 258) or daily anastrozole alone (n = 256). No difference in median overall survival was observed (37.8 versus 38.2 months; hazard ratio (HR) 1.0, 95% confidence interval (CI) 0.76 to 1.32).

The phase III SWOG0266 trial was conducted in postmenopausal women with previously untreated hormone-receptor-positive metastatic breast cancer (*13*). A total of 707 participants were randomized 1:1 to receive a loading dose followed by monthly fulvestrant plus daily anastrozole (n = 350) or daily anastrozole alone (n = 345). After a median follow-up of 35 months, median progression-free survival was 15.0 months in the fulvestrant plus anastrozole arm versus 13.5 months in the anastrozole arm (HR for progression or death with combination therapy 0.80, 95% CI 0.68 to 0.94).

The results of the meta-analysis did not show a statistically significant survival benefit for fulvestrant, but the point estimate for overall survival was in favour of the combination of fulvestrant plus aromatase inhibitors (HR 0.85, 95% CI 0.62 to 1.15, corresponding to an overall survival benefit of the combination of about 7 months in absolute terms; low-certainty evidence). There was low-certainty evidence that fulvestrant plus aromatase inhibitors might increase progression-free survival by 1 month compared to aromatase inhibitors (HR 0.89, 95% CI 0.73 to 1.08; low-certainty evidence).

Substantial heterogeneity was seen between the studies in the meta-analysis, with the FACT trial suggesting no effect and the SWOG0226 trials showing a benefit for fulvestrant. The disparity may be explained by the important difference in the type of patients included (pretreated versus treatment-naïve patients and percentage of patients with distant metastases).

Summary of evidence: harms (from the application)

Three trials provided data on adverse events and were included in the meta-analysis (*12*, *13*, *15*). The results found moderate-certainty evidence that treatment with fulvestrant plus anastrozole may or may not increase the risk of adverse events compared with treatment with anastrozole alone (risk ratio (RR) 1.03, 95% CI 0.92 to 1.15). In absolute terms, 15 more patients per 1000 patients treated might experience adverse events of grade 3 or higher with the

combination therapy, but the confidence intervals are wide (from 26 fewer to 59 more).

The most commonly reported adverse events were gastrointestinal disorders, hot flashes, headache, arthralgia and bone pain.

Additional evidence (not in the application)

Overall survival data from the SWOG0266 trial were reported after a median follow-up of 7 years in patients who did not have disease progression (*16*). Median overall survival was 49.8 months in the combination therapy group versus 42.0 months in the anastrozole group (HR for death 0.82, 95% CI 0.69 to 0.98). In the subgroup of patients who had not previously received endocrine therapy, median overall survival was 52.2 months in the combination therapy group versus 40.3 months in the anastrozole monotherapy group (HR for death 0.73, 95% CI 0.58 to 0.92). The selective crossover from the anastrozole alone group to the combination was about 45%. These data were not included in the meta-analysis conducted by the applicants.

WHO guidelines

WHO guidelines for the treatment of breast cancer are not available.

Costs/cost–effectiveness

The applicants identified two cost–utility analyses that evaluated the cost–effectiveness of fulvestrant (*17*, *18*).

A study in China compared half-dose fulvestrant plus anastrozole against full-dose fulvestrant monotherapy and anastrozole monotherapy as first-line treatment for hormone-receptor-positive metastatic breast cancer (*17*). The study used clinical input data from the SWOG0266 trial (*16*) and from a phase II randomized trial comparing fulvestrant monotherapy with anastrozole monotherapy (*19*). Compared with anastrozole monotherapy, combination half-dose fulvestrant plus anastrozole was a cost-effective alternative as the incremental cost–effectiveness ratio was US$ 15 666 per quality adjusted life year (QALY) gained, less than the willingness-to-pay threshold of US$ 29 383 in China.

Another cost–effectiveness analysis assessed fulvestrant plus anastrozole compared with anastrozole alone as first-line therapy in women with hormone-receptor-positive metastatic breast cancer from an American payer's perspective (*18*). The analysis used clinical input data from the SWOG0266 trial (*16*). The combination of fulvestrant plus anastrozole showed an incremental cost–effectiveness ratio of US$ 300 564 per QALY gained for all eligible patients and of US$ 194 450 per QALY gained for patients without previous hormonal adjuvant therapy. Applying a willingness-to-pay threshold of US$ 150 000,

addition of fulvestrant to breast cancer treatment was not considered to be cost-effective compared with anastrozole.

Coverage recommendations for fulvestrant from national reimbursement agencies vary. In Australia and Canada, reimbursement for fulvestrant has been recommended for the treatment of postmenopausal women with hormone-receptor-positive and HER2-negative unresectable advanced or metastatic breast cancer. However, reimbursement in the United Kingdom of Great Britain and Northern Ireland has not been recommended.

Availability

Fulvestrant has marketing approval from multiple national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. It is available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of fulvestrant on the EML for the treatment of metastatic breast cancer.

The Working Group noted that available data on the use of fulvestrant in first-line treatment are not yet conclusive, while its use in second-line treatment is more established and data are more mature. The meta-analysis presented in the application did not differentiate between first- and second-line use. From the meta-analysis presented, the overall survival benefit for fulvestrant (plus aromatase inhibitor) was modest but meets the threshold of survival gain endorsed by the Expert Committee. However, there was substantial heterogeneity between the included trials, postprogression therapies were unclear and the benefit not accepted unequivocally.

The Working Group also noted that the high cost of fulvestrant, the large potentially eligible patient population and variable findings in cost–effectiveness analyses were further limitations.

Committee recommendations

The Expert Committee considered that it was difficult to come to any definitive conclusion about the superiority of fulvestrant in combination with aromatase inhibitors compared with aromatase inhibitors alone. The studies included in the meta-analysis had heterogeneous results. The cumulative median overall survival gain of 7 months and median progression-free survival gain of 1 month for fulvestrant were based on low-certainty evidence.

The Committee also noted that the price of fulvestrant is very high in most settings and its cost–effectiveness is unclear.

The Committee therefore did not recommend adding fulvestrant to the EML at this time because of uncertainty in the estimates of survival benefit.

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8.2.5 Supportive medicines

Rasburicase – addition – EML and EMLc

Rasburicase **ATC Code: V03AF07**

Proposal

Addition of rasburicase to the EML and EMLc as treatment for patients with tumour lysis syndrome and as prevention in individuals at high risk of tumour lysis syndrome.

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WHO technical department

Comments were received from the WHO Department of Noncommunicable Diseases, which supported the inclusion of rasburicase on the Model Lists as it offers significant clinical value in all settings, has broad population value (about 5% of cancer patients) and has been well validated. The use of rasburicase is particularly relevant in countries where late diagnosis and greater tumour burden might increase the likelihood of tumour lysis syndrome. It will be necessary to consider issues related to safety (capacity to manage toxicities of rasburicase) and strategies to improve accessibility (e.g. dosing frequency).

EML/EMLc

EML and EMLc

Section

8.2.5 Supportive medicines

Dose form(s) & strength(s)

Powder and solvent for solution for infusion: 1.5 mg, 7.5 mg in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Rasburicase had not previously been considered for inclusion on the Model Lists.

Allopurinol is currently included on the EMLc for the prevention and treatment of tumour lysis syndrome in children. It has not been considered for inclusion on the EML for treatment of adults for this indication.

Public health relevance (burden of disease)

Tumour lysis syndrome is an oncological emergency characterized by a group of metabolic disturbances including hyperkalaemia, hyperphosphataemia, hypocalcaemia and hyperuricaemia. In particular, hyperuricaemia may lead to renal damage and end-stage renal failure.

The exact incidence of tumour lysis syndrome is unknown since its frequency varies with the underlying malignancy and the specific definition used. Some definitions include only laboratory abnormalities such as plasma levels of potassium, phosphate, calcium or uric acid. Under these definitions, the incidence of laboratory abnormalities can be as high as 45% of patients as it has been observed in small cohorts of children with acute lymphoblastic leukaemia (*1*, *2*). In broader populations, however, the incidence of a laboratory tumour lysis syndrome has been estimated in around 10–15% of patients (*3*, *4*). Only a small proportion of patients with laboratory abnormalities ultimately develop clinical symptoms, such as nausea, muscle cramps, weakness or fatigue. The reported incidence of clinical tumour lysis syndrome is around 4–6% (*3*, *5*, *6*).

Tumour lysis syndrome is far more frequent in haematological malignancies, although it has also been reported in solid tumours, especially in gastrointestinal and lung cancers (*7*). In general, the risk of tumour lysis syndrome is higher in cancers with a high proliferative rate and rapid response to therapy.

Treating the complications of tumour lysis syndrome is very resource intensive, particularly for hyperuricaemia, which may lead to renal complications and the need for renal-replacement therapies. Therefore, in low- and middle-income settings, the use of rasburicase might result in net savings, especially with shortened regimens (*8*–*10*).

Summary of evidence: benefits (from the application)

The applicants conducted a literature search for randomized trials and systematic reviews of rasburicase and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool and judgements about the certainty of the evidence were made following the GRADE approach.

Three systematic reviews (*11*–*13*) and two randomized trials were identified (*14*, *15*).

One trial included 280 adults with leukaemia or lymphoma. Participants were randomized to rasburicase, allopurinol or a combination of rasburicase plus allopurinol. All the interventions were given for 5 days after receiving chemotherapy (*15*). The other trial included 52 children with leukaemia or lymphoma, who were randomized to rasburicase or allopurinol for 5 to 7 days, also after receiving chemotherapy (*14*). Both trials focused on uric acid levels and were not powered to detect differences in patient-relevant outcomes.

In both trials, plasma uric acid levels decreased faster with rasburicase: 4 hours after the first dose, uric acid decreased by 86–88% with rasburicase compared with 12–14% with allopurinol. This finding reflects the mechanism of action of the drugs: rasburicase can effectively reduce uric acid levels, while allopurinol can only prevent the formation of new uric acid.

Only one trial reported data to estimate the effect of rasburicase on the incidence of tumour lysis syndrome and patient-relevant outcomes (*15*). Compared with allopurinol, rasburicase may reduce the incidence of laboratory tumour lysis syndrome (risk ratio (RR) 0.51, 95% confidence interval (CI) 0.33 to 0.79; in absolute terms, 222 fewer events per 1000 patients, 95% CI 94 fewer to 301 fewer; very-low-certainty evidence). However, evidence of the effect of rasburicase on clinical tumour lysis syndrome or renal failure was less clear (RR 0.74, 95% CI 0.17 to 3.22 and RR 0.98, 95% CI 0.14 to 6.87, respectively; both very-low-certainty evidence).

Summary of evidence: harms (from the application)

Compared with allopurinol, rasburicase might increase the risk of adverse events (RR 3.96, 95% CI 0.45 to 34.7; in absolute terms, 33 more events per 1000, 95% CI 6 fewer to 371 more; very-low-certainty evidence).

The events observed with rasburicase were mainly hypersensitivity reactions such as rash, arthralgia or injection-site irritation. They were generally mild and lead to a discontinuation of the drug in only one out of 92 participants (*15*).

Additional evidence (not in the application)

As regards dosage, a meta-analysis of 10 studies compared efficacy and cost-savings of a single-dose regimen of rasburicase (at doses ranging from 3 mg to

7.5 mg (fixed dose) or 0.05 mg/kg to 0.20 mg/kg (weight-based dose) versus the daily dosing of 0.2 mg/kg for 5 days approved by the United States Food and Drug Administration in adult patients with hyperuricaemia or at high risk of tumour lysis syndrome (*16*). There was no significant difference in response rates between the pooled single-dose rasburicase arm and the daily dose rasburicase arm (88.2% versus 90.2%; odds ratio (OR) 0.81, 95% CI 0.41 to 1.60). When only studies using single-dose rasburicase at standard doses (6–7.5 mg fixed dose or 0.15–0.20 mg/kg weight-based dose) were considered, the pooled response rate was 91.8%. Moreover, single dose administration of standard-dose rasburicase was associated with important cost savings. Wholesale drug acquisition prices for the different treatment regimens were about US$ 4500 for single standard-dose rasburicase versus about US$ 36 000 for daily-dose rasburicase.

The use of rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to observations of severe haemolysis during clinical trials (*17*). Haemolytic anaemia is likely to occur in G6PD-deficient patients because of their inability to break down hydrogen peroxide, a by-product of the oxidation of uric acid. Testing to identify patients with G6PD deficiency is recommended before treatment with rasburicase. In emergency settings where G6PD deficiency cannot be determined, monitoring for signs and symptoms of haemolytic anaemia is recommended and supportive care (e.g. haemodialysis) must be available.

WHO guidelines

WHO guidelines for the management of tumour lysis syndrome are not available.

Costs/cost–effectiveness

The applicants identified four studies: one cost–benefit analysis (*18*), two cost–effectiveness analyses (*19*, *20*) and one cost–consequence study (*21*).

Three of the four studies identified were considered to have serious limitations and their results were judged unreliable (*18*, *20*, *21*). These studies did not use an appropriate mathematical model nor a probabilistic sensitivity analysis. In addition, they had several errors or omissions and some assumptions were not shown or were incorrect.

Only one study, a cost–effectiveness study in China, had acceptable quality. It used a decision tree as the model method, from a perspective of the Chinese health care system (*19*). The study considered the use of rasburicase in the prevention and treatment paediatric patients with acute myeloid leukaemia, acute lymphoid leukaemia or non-Hodgkin lymphoma. The results suggested that rasburicase was cost-effective in most of the scenarios, with an incremental cos–effectiveness ratio between US$ 991 and US$ 2031 per quality-adjusted life year (QALY) as treatment and US$ 5391 and US$ 17 580 per QALY as prophylaxis.

Availability

Rasburicase has wide global marketing and regulatory approval.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the inclusion of rasburicase on the EML and EMLc for the treatment and prevention of tumour lysis syndrome. The available evidence shows rasburicase to be more effective than allopurinol in reducing plasma uric acid levels, and it can be used for treatment as well as prevention of tumour lysis syndrome (allopurinol is used only for prevention). Evidence for benefit for clinical outcomes (e.g. mortality, renal failure) is less clear, but in this context the benefit of rasburicase is undisputed for reducing uric acid (e.g. a surrogate outcome considered reasonably likely based on therapeutic and pathophysiological evidence); to predict clinical benefit; and to avoid clinical sequalae. Treating tumour lysis syndrome once it occurs is very resource intensive so effective preventative measures are desirable.

In terms of safety, of particular concern is the risk of severe haemolysis, and rasburicase should not be given to patients with G6PD deficiency. Thus, testing to identify patients with G6PD is required. In emergency settings, where G6PD deficiency cannot be determined, rasburicase should only be used when haemodialysis is available.

Careful patient selection to limit the use of rasburicase to patients most likely to benefit (e.g. at high risk of tumour lysis syndrome) and less likely to experience adverse effects (e.g. G6PD deficiency) will also be important at the country level.

The Working Group acknowledged the high cost rasburicase, and also noted the potential for cost savings by using single-dose administration rather than daily dose administration over several days, without significantly compromising benefit.

Committee recommendations

The Expert Committee acknowledged that tumour lysis syndrome is an oncological emergency for which prevention and treatment are critical to avoid severe acute kidney injury, which is resource-intensive to treat and may be fatal.

The Committee noted that only allopurinol is currently included on the Model Lists for tumour lysis syndrome. Allopurinol, while inexpensive and administered orally, is only effective for the prevention of tumour lysis syndrome by inhibiting the formation of new uric acid; it does not eliminate already formed uric acid. It therefore takes several days to have an effect on uric acid levels. The Committee noted that allopurinol is associated with xanthinuria (deposition of xanthine crystals in the renal tubules and associated acute kidney

injury), and can interact with several medicines, including chemotherapeutic agents, antibiotics and diuretics.

The Committee noted that rasburicase, which is a recombinant version of urate oxidase, works by metabolizing uric acid to a more water-soluble metabolite. Rasburicase can markedly and rapidly decrease uric acid levels and prevent other complications of tumour lysis syndrome (such as end-stage renal failure and need for life-long dialysis). It therefore offers a significant advantage for the management of paediatric and adult patients at high risk of tumour lysis syndrome, especially those with impaired renal or cardiac function, and for patients with pre-existing hyperuricaemia. From the meta-analysis presented in the application, the Committee noted that rasburicase may halve the risk of laboratory tumour lysis syndrome compared with allopurinol.

The Committee noted that rasburicase is well tolerated. However, it should not be given to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency because hydrogen peroxide, a by-product of uric acid breakdown, can cause severe haemolysis in these patients. Patients at risk of G6PD deficiency (e.g. prior medicine-induced haemolytic anaemia, ethnic background associated with high prevalence of G6PD deficiency) should be tested for G6PD deficiency, preferably before administration of rasburicase.

The Committee noted that rasburicase is expensive, especially when used according to the dosage approved by the United States Food and Drug Administration and the European Medicines Agency, which is 0.2 mg/kg a day for up to 5 days. The Committee acknowledged numerous experimental studies showing that a single dose of rasburicase is as effective in lowering uric acid levels as approved daily dosing of rasburicase for 5 days, and this dosing is associated with considerable cost savings. The Committee considered that the high cost of rasburicase could be reduced by using single-dose administration and using it only in selected high-risk patients.

The Expert Committee therefore recommended inclusion of rasburicase on the complementary list of the EML and EMLc for the prevention and treatment of tumour lysis syndrome in high-risk patients. However, noting the high price of rasburicase, the Committee considered that the single-dose administration strategy for rasburicase is the preferred dosing option, based on evidence of similar response rates and greatly reduced costs.

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CAR-T cell therapy – review

Axicabtagene ciloleucel (*axi-cel*) ATC Code: L01XX70
Tisagenlecleucel (*tisa-cel*) ATC Code: L01XX71

Proposal

To review chimeric antigen receptor (CAR)-T cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Addition of CAR-T cell therapy to the Model List is not proposed at this time.

Applicant

Department of Internal Medicine, University Hospital of Cologne, Cologne, Germany

Cochrane Haematology

Cochrane Cancer

WHO technical department

WHO Department of Health Products Policy and Standards

EML/EMLc

Not applicable

Section

Not applicable

Dose form(s) & strength(s)

Not applicable

Core/complementary

Not applicable

Individual/square box listing

Not applicable

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Over the past decade, CAR-T cell therapy directed against B-lymphocyte antigen CD19 has emerged as another treatment option for relapsed or refractory DLBCL, an aggressive disease with limited median overall survival (less than 6–12 months). The overall process of treating DLBCL with CAR-T

cells is so complex that it limits feasibility and large-scale uptake. First, T-cells are collected from the patient's blood before they are genetically altered and multiplied ex vivo to express a modified antigen receptor that directs the lymphocytes against the tumour cells. The receptors are called chimeric because they are engineered to combine functions related to tumour recognition of antibodies and antitumour T cell activation into a single receptor. These chimeric receptors can recognize antigens independent of major histocompatibility complex presentation.

Before returning the altered cells to the patient, it is recommended that the patient receives lymphodepletion chemotherapy with fludarabine and cyclophosphamide (*1–4*) to improve treatment efficacy (*5*, *6*). The altered and multiplied cells are then returned to the patient via intravenous infusion (*7*, *8*). After infusion, patients should be monitored daily during the first 10 days and be near the clinic for at least 4 weeks to monitor the occurrence of frequent and potentially severe adverse events (*1*, *2*, *9*, *10*). At present, the entire process is prohibitively expensive.

Public health relevance (burden of disease)

Global data on the incidence and mortality of DLBCL are few. In 2015, the age-adjusted incidence rate of DLBCL in the United States was 5.5 per 100 000 people per year, the mortality was 1.8 per 100 000 people per year, and the median age at diagnosis was 65 years (*11*). Males are at a 1.5 times higher risk of being diagnosed with DLBCL (*12*, *13*). The incidence also varies by ethnicity and geographic region.

Untreated, DLBCLs are associated with a median survival of less than 1 year. With first-line treatment (often the combination of the anti-CD20 antibody rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (*14*) – all on the EML), patients may have good outcomes (*13*). But 30–40% of patients experience relapse or their disease is refractory to first-line treatment. The treatment of relapsed/refractory DLBCL is complex; it depends on factors such as the fitness of the patient to tolerate aggressive chemotherapy and location of the disease (e.g. presence of central nervous system involvement), and includes autologous haematopoietic stem cell transplantation. Even after second-line treatment (salvage chemotherapy followed by autologous stem cell transplantation), about 50% of patients still experience relapse (*15*).

Summary of evidence: benefits (from the application)

The review presented the preliminary results of a Cochrane systematic review (in development) assessing the benefits and harms of CAR-T-cell therapy for relapsed/refractory DLBCL (*16*).

Characteristics of the studies

Thirteen studies evaluated the efficacy and safety of CAR-T cells in people with relapsed/refractory DLBCL. Ten trials were single-arm studies of CAR-T-cell therapy without a control group (*17–26*); three trials included multiple arms of either varying doses of CAR-T cells alone (*27*, *28*) or varying doses of CAR-T cells combined with other agents (*29*). The number of participants that received CAR-T cells ranged from 15 (*29*) to 269 participants (*28*), and three trials included more than 100 participants receiving CAR-T cells (*20*, *25*, *28*).

Interventions

Anti-CD19 directed CAR-T cells were used in 11 studies (*17–20*, *22*, *24–29*), while two studies used a combination of anti-CD19 and anti-CD20 (*21*) or anti-CD22-directed CAR-T cells (*23*). In most trials, participants received a single infusion of CAR-T cells; co-interventions consisted of use of the immune checkpoint inhibitors durvalumab (*29*) and atezolizumab (*26*).

In all trials, participants received lymphodepleting chemotherapy before the infusion of CAR-T cells (mostly fludarabine and cyclophosphamide; but the participants in four studies (*20–23*) received other combinations).

Participants

Three studies (*20*, *21*, *26*) included participants with relapsed/refractory DLBCL only. In contrast, most studies (*17–19*, *22–25*, *27–29*) also included participants with other haematological malignancies such as acute lymphoblastic leukaemia, Burkitt lymphoma, mantle cell lymphoma, follicular lymphoma or primary mediastinal large B-cell lymphoma.

Outcomes

Four studies were at high risk of confounding by indication/selection, either because the median age of the study group was substantially younger than average (38–40.5 years compared with median age of diagnosis for DLBCL of about 70 years) (*17*, *18*), or males were underrepresented in the study group (39% while about 55% of all patients with DLBCL are male) (*23*), or participants had a prelymphodepletion status potentially associated with better progression-free survival (*19*).

All studies were unblinded and therefore at high risk of performance and detection bias for outcomes. All reported outcomes except for overall survival (i.e. investigator-assessed and patient-reported outcomes) were subjective to a greater or lesser extent and therefore at high risk of bias.

Attrition bias (incomplete outcome data) was analysed as to whether studies assessed outcomes for all enrolled participants. Attrition bias was evaluated separately for the following three outcome categories.

- *Overall survival* – Two studies (*18*, *26*) were at unclear risk of bias. The number of enrolled participants was not reported in the published abstract (only the number of participants who received CAR-T-cell therapy and atezolizumab). Six studies (*20–23*, *25*, *28*) were judged to be at high risk of bias because outcomes were reported only for a subset of the enrolled participants.
- *Response* – Only one study was judged to be at low risk of bias because the objective response and complete response were reported for all participants who underwent leukapheresis (*28*). Three studies were judged to be at unclear risk of bias (*18*, *26*, *27*). Nine studies (*17*, *19–25*, *29*) were judged to be at high risk of bias because outcomes were reported only for a subset of the enrolled participants.
- *Quality of life* – The two studies that reported quality of life were both judged to be at high risk of bias (*20*, *28*).

Regarding the definition of the outcomes, bias was assessed separately for three outcomes.

- *Overall survival* – Due to the objective nature of the outcome, all studies that reported overall survival were at low risk of bias (*18*, *20–23*, *25*, *26*, *28*).
- *Response* – Seven studies were judged to be at low risk of bias (*20–26*) because the authors specified criteria used for response assessment and either reported time-point specific outcomes or reported the timing of assessment for all reported outcomes. The remaining six studies were at high risk of bias (*17–19*, *27–29*).
- *Quality of life* – The two studies that reported quality of life were judged to be at low risk of bias as both used standardized scales (*20*, *28*).

Efficacy

Overall survival

Data on overall survival were reported for eight of the included studies (*18*, *20–23*, *25*, *26*, *28*). The reported results were limited to time-point specific rates only, given that there was large heterogeneity in study sample sizes and follow-up durations between the studies.

Survival rates at 6 months were reported as 75% (95% confidence interval (CI) 69% to 80%; 256 participants, 80.4% DLBCL) (*28*) and 78% (95% CI 69% to 85%; 108 participants; proportion of DLBCL unclear but above 70%) (*25*).

One study (*18*) provided 10 months overall survival results of 55% (95% CI 39% to 74%) for 13 individuals, 12 (92%) of whom had DLBCL. The 12-month

survival rates, which were reported for three studies (*20*,*25*,*28*) ranged between 48% (95% CI 38% to 57%; 99 participants) (*20*) and 59% (95% CI 49% to 68%; 108 participants; proportion of DLBCL unclear, but above 70%) (*25*).

Data for survival at 18 months were available from two studies which reported survival rates of 43% (95% CI 33% to 35%; 99 participants) (*20*) and 52% (95% CI 41% to 62%; 108 participants; proportion of DLBCL unclear, but above 70%) (*25*). The estimated survival at 24 months was 51% (95% CI 40% to 60%) for 101 participants, including 77 (76%) individuals with DLBCL (*25*).

Progression-free survival

Eight studies reported results on progression-free survival, disease-free survival or relapse-free survival. Results for progression-free survival at 6 months were reported in two studies: 49% (95% CI 39% to 58%; 101 participants, 76% DLBCL) (*25*) and 51% (95% CI 45% to 58%; 256 participants, 80.4% DLBCL) (*28*). Twelve months progression-free survival was reported in four studies; it ranged from 44% (95% CI 34% to 53%; 101 participants, 76% DLBCL) (*25*) to 75% (95% CI 46% to 90%; 16 participants with DLBCL) (*23*). One study reported a progression-free survival rate of 63.3% for 22 participants, including 17 (77%) individuals with DLBCL, but did not report a corresponding confidence interval (*27*).

At 12 and 18 months, one study reported a relapse-free survival rate of 64% (95% CI 48% to 76%) for 99 participants with DLBCL (*20*).

Overall response rate

Overall, 12 studies (*17*,*19*–*29*) reported data on overall response rates, but with substantial variability in follow-up durations and outcome definitions. One study reported an overall response rate of 80% (95% CI 56% to 94%) for 20 participants with DLBCL at 1 month of follow-up (*24*).

Overall response rates at 3 months of follow-up were reported in three studies (*21*,*22*,*24*); they ranged from 50% (95% CI 49% to 79%; 14 participants with DLBCL) (*22*) to 81% (95% CI 58% to 95%; 21 participants with DLBCL) (*21*).

At 6 months, in two studies, the overall response rate was sustained for 45% (95% CI 23% to 69%; 20 participants with DLBCL) of participants (*24*) and for 46% (95% CI 19% to 75%; 21 participants with DLBCL) (*21*).

Quality of life

Two studies reported on quality of life using a number of validated tools for several time points (*30*,*31*). In the first study, FACT-Lym total scores (range 0–168, higher scores indicate better quality of life) and Short Form-36 (SF-36) Health Survey (range 0–100, higher scores indicate better quality of life) were reported at baseline and changes from baseline were reported at months 3, 6, 12 and 18 (*30*). Improvements were above the clinically meaningful minimal

important differences at months 3, 6 and 12 and 18, as assessed by both instruments. Improvements were reported in all domains. For instance, the largest mean change from baseline occurred for functional, physical and social/family FACT-G domains after 18 months; the higher mean change from baseline in the emotional domain was reported after 12 months. Most of the patient-reported quality of life assessments were completed by patients with a clinical response. Non-responders died or withdrew from the study to follow alternative therapies and did not complete the serial quality-of-life assessments.

In the second study, EORTC QLQ-C30 scores (range not reported; minimal important difference was defined a priori as a ±10-point change from baseline) and EQ-5D-5L VAS scores (range 0–100, minimal important difference defined as an increase or decrease from baseline of ≥ 0.07; higher scores indicate better quality of life) were reported at baseline and months 1, 2, 3, 6, 9 and 12 (*31*). The number of participants evaluated decreased over time, with only 38 participants left for assessment at month 12 from 186 participants at baseline. Mean (SD) EQ-5D-5L VAS scores increased from 68.3 (19.5) at baseline to 82.1 (17.8) at month 12. In general improvements in quality of life and fatigue were detected as early as 2 months after liso-cel infusion, were clinically relevant and continued to be maintained 18 months after infusion.

Certainty of the evidence

Using the GRADE approach, the reviewers rated the certainty of the evidence as very low for all outcomes. They did not do a meta-analysis of the data because the trials identified had either a single arm or multiple arms of CAR-T-cell therapy without a control group.

In summary, the prognosis for people with heavily pretreated relapsed/refractory DLBCL who are not candidates for autologous stem-cell transplantation, or people who relapse after autologous stem-cell transplantation, is generally poor. In a small number of study participants, CAR-T-cell therapy was associated with a median overall survival well above 12 months, reaching 24 months in about half of the cases. Confidence in the data is low due to the lack of a control group and limited internal and external validity.

Summary of evidence: harms (from the application)

Characteristics of the studies

Among the studies reporting adverse events, eight were judged to be at low risk of bias because all or most outcomes were reported for most participants receiving CAR-T cells. Five studies reported outcomes for all participants receiving CAR-T cells (*20–23*, *27*). In three studies, adverse events were not reported for the entire cohort of treated patients but missing data were few and did not affect risk of bias (*25*, *26*, *28*).

One study was judged to have an uncertain risk of bias because the number of participants receiving CAR-T cells was unclear due to insufficient reporting of the flow of participants (*18*). Two studies were judged at high risk of bias. In one, outcomes were reported only for participants receiving CAR-T cells and durvalumab (i.e. for 11 out of 15 (73%) participants receiving CAR-T cells) (*29*). In the other, only half of the safety outcomes of interest (cytokine release syndrome and neurotoxicity) were reported for all 32 participants receiving CAR-T cells, while half of the safety outcomes of interest (use of tocilizumab and/or corticosteroids and cytopenia) were reported for 10 out of 32 (31%) participants receiving CAR-T cells only (*24*).

Findings

Any adverse events

The number of participants with any adverse events was reported in five studies (550 participants). Adverse events occurred frequently, with 99% of participants in one study reporting any adverse event (*28*) and all participants reporting any adverse events in the other four studies (*20*, *23*, *25*,*26*). The same studies reported the percentage of participants with any adverse event at grade ≥ 3, which ranged between 68% (*23*) and 98% (*25*).

Any serious adverse events

Four studies (281 participants) reported the number of participants with any serious adverse events. In three studies (*20*, *25*, *26*), 56% to 68% of participants had serious adverse events; in another, no serious adverse events were reported (*23*). Only one study reported the percentage of participants with any serious adverse event at grade ≥ 3 (48%) (*25*).

Cytokine release syndrome

The number of participants having any grade or grade ≥ 3 cytokine release syndrome was reported in 11 studies (675 participants) which used different grading criteria (*18*, *20–29*).

Five studies that used criteria described by Lee and colleagues (*32*) reported between 42% and 100% of participants having cytokine release syndrome (*21*, *23–25*, *28*). The proportion of participants with grade ≥ 3 cytokine release syndrome ranged between 1% (*24*) and 29% (*21*). Using the University of Pennsylvania grading scale (*33*), one study reported 58% and 22% of participants had cytokine release syndrome of any grade, and grade ≥ 3, respectively (*20*). According to one study, 69% of participants had cytokine release syndrome with a fever higher than 39.0 °C (*18*). One study reported that cytokine release syndrome did not occur after the infusion of durvalumab (*29*).

Neurotoxicity

Ten studies (664 participants) reported neurotoxicity of any grade or grade ≥ 3 (*20–29*). The occurrence of neurotoxicity was in a range of 16% to 100% of participants. Grade ≥ 3 neurotoxicity was reported in 0% (*23*, *24*, *29*) to 55% (*27*) of participants.

Some authors reported using tocilizumab and/or corticosteroids to treat cytokine release syndrome and/or neurotoxicity. Seven studies (495 participants) reported the number of participants treated with tocilizumab and/or corticosteroids (*21–25*, *27*, *28*). Between 0% and 80% of participants received tocilizumab alone or without further specification (*21–25*, *27*, *28*). Between 3% and 67% of participants received tocilizumab and corticosteroids, such as dexamethasone (*20*, *23*, *25*, *28*). Between 0% and 20% received corticosteroids alone (*21*, *22*, *24*, *27*, *28*). In one study, prophylactic use of tocilizumab was introduced in phase II (cohort 3) (*25*).

Cytopenias

Cytopenias of any grade or grade ≥ 3 were reported in eight studies (625 participants), usually reported as anaemia, leukopenia, neutropenia and thrombocytopenia (*20*, *21*, *23–28*). Three studies also reported prolonged cytopenias lasting longer than 28 days (*20*, *25*, *28*). The percentage of participants with grade ≥ 3 prolonged cytopenias was 34% (*20*), 37% (28) and 30% (*25*).

Febrile neutropenia

The number of participants with febrile neutropenia was reported in five studies (531 participants) (*20*, *21*, *25*, *27*, *28*). Febrile neutropenia occurred in between 9% (*28*) and 76.2% (*21*) of participants. Grade ≥ 3 febrile neutropenia occurred in between 9% (*28*) and 50% (*27*) of participants.

Any infections

Three studies (488 participants) reported the participants having any infection (531 participants) (*20*, *25*, *28*). One study reported that 34% of participants had infections of any grade (*20*). Grade ≥ 3 infections occurred in 20% (*20*), 12% (*28*) and 28% (*25*) of participants.

Additional evidence (not in the application)

The Cochrane review upon which the application is based was published in September 2021, after the Expert Committee meeting (*34*).

WHO guidelines

WHO guidelines for treatment of relapsed/refractory DLBCL are not available.

Costs/cost–effectiveness

Treatment with CAR-T cells is technologically demanding and resource-intensive. It requires well-equipped facilities to produce CAR-T cells and trained physicians to administer the treatment and adequately follow up patients for management of adverse events. The global availability of CAR-T-cell therapy is limited and confined to a few tertiary oncology centres. Data on comparative effectiveness and cost–effectiveness are limited to a few high-income countries.

Treatment with the CAR-T-cell therapies axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) consists of a single-use per year per patient (*1*, *2*). The listed price for axi-cel was reported to be US$ 375 000 in the United States (*35*) and € 327 000 in Germany (*36*). The overall estimated costs per case varies between US$ 552 921 and US$ 655 000 (*37*, *38*). The listed price (i.e. actual price without discount) for tisa-cel is US$ 475 000 in the United States, and € 320 000 in Germany (*39*). The estimated overall costs of tisa-cel per case were between US$ 382 702 and US$ 529 000 (*37*, *40*). Yearly therapy costs in Germany were estimated to range between € 282 420 and € 283 245 (*41*).

The additional cost to the budget of the United States health care system was estimated at US$ 12 billion for axi-cel and US$ 9 billion for tisa-cel a year, if these treatments were given to all eligible patients (*37*).

The reported cost–effectiveness of axi-cel varied greatly, with incremental cost–effectiveness ratios ranging from < US$ 50 000 to US$ 159 000 per quality-adjusted life year (QALY) gained. The report of the National Institute for Health and Care Excellence (NICE) in the United Kingdom of Great Britain and Northern Ireland also noted an incremental cost–effectiveness ratio between < £ 50 000 and > £ 100 000 per QALY gained and its use within the Cancer Drugs Fund was recommended (*42*). An incremental cost–effectiveness ratio of € 44 746 per QALY gained was reported over a life-time horizon in a study in Italy (*43*, *44*).

Incremental cost–effectiveness ratio for tisa-cel varied between US$ 42 000 up to US$ 508 530 per QALY gained, depending on the time horizon and perspective of the analyses (*37*, *45*, *46*). NICE reported incremental cost–effectiveness ratios per QALY gained between £ 42 991 and £ 55 403, based on a confidential commercial discount; it did not recommend tisa-cel for routine use in the National Health Service. Use within the Cancer Drugs Fund was recommended (*47*).

Availability

Two types of anti-CD19 CAR-T-cell therapy are currently commercially available: axi-cel and tisa-cel.

Axi-cel is approved by the Australian Government (*48*), the European Medicines Agency (*9*), Health Canada (*49*) and the United States Food and

Drug Administration (*4*) for the treatment of: relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified; primary mediastinal large B-cell lymphoma; high-grade B-cell lymphoma; and DLBCL arising from follicular lymphoma.

Tisa-cel is approved by the Australian Government (*50*), the European Medicines Agency (*10*), Health Canada (*51*) and the United States Food and Drug Administration (*3*) for the following indications.

- Adult patients with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia that is refractory or in second or later relapse.

The Australian Government and Health Canada also included tisa-cel for paediatric patients with B-cell precursor acute lymphoblastic leukaemia who have relapsed following allogeneic stem-cell transplant or are otherwise ineligible for stem-cell transplant (*50*, *51*).

Other considerations

The proposed dosage for tisa-cel is independent of weight and is $0.6–6.0 \times 10^8$ CAR-positive, viable T-cells given intravenously (*2*, *10*). For axi-cel the proposed dosage depends on the patient's body weight. A dose of 2×10^6 CAR-positive T-cells per kg body weight with a maximum dose of 2×10^8 CAR-positive viable T-cells is recommended (*1*, *9*).

Both substances must only be administered in a specialized treatment centre by trained health care professionals. These professionals need experience in treating haematological malignancies and must be trained on the administration and management of patients treated with each CAR-T substance (*1*, *2*, *9*, *10*).

The application noted that numerous ongoing trials are evaluating CAR-T-cell therapy for people with relapsed/refractory DLBCL; three are randomized controlled trials that will be primarily completed between 2022 and 2025 (BELINDA (*52*), TRANSFORM (*53*) and ZUMA-7 (*54*)).

Committee recommendations

The Expert Committee considered the review of the available evidence for chimeric antigen receptor (CAR)-T-cell therapy for treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and noted that inclusion of CAR-T-cell therapies on the Model Lists was not proposed at this time.

The Committee noted that CAR-T-cell therapy is highly specialized, requiring dedicated health system resources well beyond those available in most settings at this time. Current treatment and management costs are also prohibitively high, and exceed affordability thresholds in almost all countries.

The Committee considered that CAR-T-cell therapies are an area of great interest and therapeutic relevance in the treatment of DLBCL, and potentially other diseases. The Committee acknowledged that at present, the available evidence is limited and of very low certainty. Nevertheless, it was noted that the immature data from multiple studies indicate that CAR-T-cell therapy can induce durable complete responses, which may lead to clinical cures in some patients. Currently, the main uncertainties about the clinical benefits of CAR-T-cell therapy relate to the proportion of patients achieving long long-term disease-free survival, and when CAR-T-cell therapy is best used in the overall treatment algorithm. Safety concerns include cytokine release syndrome and neurological toxicity, both of which occur in a high proportion of patients, may be life-threatening and require highly specialized medical management. Data on long-term safety are currently limited.

The Committee acknowledged that the field of CAR-T-cell therapy is rapidly evolving, with many ongoing studies that might address the existing clinical uncertainties. The application of this treatment could be advantageous in low- and middle-income settings: a potential curative treatment for haematological malignancies with a single infusion of CAR-T cells might be a competitive therapeutic option when compared with multiple chemotherapy regimens administered in hospitals over longer periods of time.

The Committee considered that evidence on these therapies should continue to be monitored by WHO. The Committee advised that it would welcome an updated review of the evidence for CAR-T-cell therapy for consideration at a future meeting. WHO will need to have a strong leadership and advocacy role in facilitating affordable and equitable access to these treatments.

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Section 13: DERMATOLOGICAL MEDICINES

13.4 Medicines affecting skin differentiation and proliferation

Calcipotriol – addition – EML and EMLc

Calcipotriol **ATC Code: D05AX02**

Proposal

Addition of calcipotriol on the core list of the EML and EMLc for the treatment of plaque-type psoriasis.

Applicant

International League of Dermatology Societies

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

13.4 Medicines affecting skin differentiation and proliferation

Dose form(s) & strength(s)

Cream or ointment: 0.005% (50 micrograms/mL)
Lotion: 0.005% (50 micrograms/mL)

Core/complementary

Core

Individual/square box listing

Square box listing for calcipotriol as the representative medicine, with calcitriol and tacalcitol as therapeutic alternatives.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Calcipotriol has not been previously considered for inclusion on the EML and EMLc.

The EML and EMLc currently include betamethasone valerate and hydrocortisone acetate cream or ointment, 5% coal tar solution and 5% salicylic acid solution for the treatment of psoriasis.

Public health relevance (burden of disease)

Psoriasis affects people around the world, but its prevalence varies considerably, ranging from 0.09% in the United Republic of Tanzania to over 10% in Norway (*1*). At least 60 million people are estimated to be affected worldwide (*2*, *3*).

Psoriasis varies in morphology, distribution, severity and course. The condition can first occur at any age: it has been reported in newborns and in elderly people. The most common age at onset for the first occurrence of psoriasis ranges from 15 to 20 years, followed by 55 to 60 years (*1*, *4*). The most common form of psoriasis is plaque psoriasis in which sharply defined, round/oval or nummular (coin-sized) plaques may be seen. This form accounts for 80–90% of cases of psoriasis (*1*). People with psoriasis have a lower quality of life than healthy people without the condition, and similar to, or worse than, people with other chronic diseases (*4*, *5*).

Summary of evidence: benefits (from the application)

Systematic reviews

A 2013 Cochrane systematic review of 177 studies (34 808 participants) compared the effectiveness, tolerability and safety of topical treatment for chronic plaque psoriasis versus placebo, and of vitamin D analogues with other topical treatments (*6*).

Vitamin D analogues versus placebo

Twenty trials of vitamin D analogues (10 using calcipotriol, six using calcitriol and two using tacalcitol) for body psoriasis included 3771 participants. Primary efficacy outcomes included: investigator's assessment of overall global improvement or investigator's global assessment of disease severity (IAGI/IGA); total severity scores; psoriasis area and severity index (PASI); patient assessment of overall global improvement or patient global assessment of disease severity (PAGI/PGA); and a combined endpoint of these four measures. Pooled results (standardized mean difference (SMD), 95% confidence interval (CI)) for all treatments combined, and for calcipotriol, calcitriol and tacalcitol are presented in Table 7.

Table 7
Efficacy of vitamin D analogues compared with placebo in treatment of psoriasis: pooled results of 20 trials

Treatment	SMD (95%CI)				
	IAGI/IGA	Total severity scores	PASI	PAGI/PGA	Combined
All treatments	–0.95 (–1.17 to –0.74)	–1.04 (–1.33 to –0.74)	–0.58 (–0.71 to –0.45)	–0.54 (–0.72 to –0.36)	–0.90 (–1.07 to –0.72)
Calcipotriol	–0.93 (–1.17 to –0.68)	–1.15 (–1.41 to –0.89)	–0.65 (–0.75 to –0.55)	–0.64 (–0.97 to –0.30)	–0.96 (–1.15 to –0.77)
Calcitriol[a]	–1.03 (–1.71 to –0.36)	–1.22 (–2.38 to –0.07)	–	–0.59 (–0.76 to –0.41)	–0.92 (–1.54 to –0.29)
Tacalcitol	–0.84 (–1.41 to –0.26)	–0.66 (–0.95 to –0.36)	–0.27 (–0.56 to 0.03)	–0.24 (–0.53 to 0.05)	–0.73 (–1.09 to –0.37)

SMD: standardized mean difference; CI: confidence interval; IAGI/IGA: investigator's assessment of overall global improvement or investigator's global assessment of disease severity; PAGI/PGA: patient assessment of overall global improvement or patient global assessment of disease severity; PASI: psoriasis area and severity index.

[a] The authors noted that there was considerable variation between-studies in the IAGI SMD for calcitriol. The pooled effect was –1.03 (95% CI –1.71 to –0.36), but this ranged from –0.26 (95% CI –0.99 to 0.47) to -3.11 (95% CI –3.57 to –2.66).

Vitamin D analogues versus potent topical corticosteroids

Eight studies (2655 participants) reported efficacy data for three vitamin D analogues (calcipotriol, calcitriol and tacalcitol) versus potent corticosteroids (betamethasone dipropionate, betamethasone valerate, desoximetasone, diflorasone diacetate and fluocinonide). Overall, no statistically significant difference was found between vitamin D analogues and potent corticosteroids for the primary efficacy outcomes. The SMD across all six treatment comparisons for IAGI was 0.17 (95% CI –0.04 to 0.37).

For the outcome of IAGI/IGA, one study showed that calcipotriol was significantly better than fluocinonide (SMD –0.58, 95% CI –0.99 to –0.18). Calcipotriol was significantly less effective than both diflorasone diacetate 0.05% ointment (SMD 0.27, 95% CI 0.02 to 0.52) and betamethasone dipropionate (SMD 0.43, 95% CI 0.28 to 0.58). No statistically significant differences were observed between calcipotriol and betamethasone valerate, calcitriol and betamethasone dipropionate, or calcitriol and betamethasone valerate.

Comparisons of different vitamin D analogues

Three trials (498 participants) contributed IAGI/IGA data for comparisons of different vitamin D analogues. The analysis found a significant difference in

favour of calcipotriol versus tacalcitol (SMD –0.47, 95% CI –0.73 to –0.21), but not versus calcitriol (SMD 0.00, 95% CI –0.25 to 0.25) or maxacalcitol (SMD 0.43, 95% CI –0.12 to 0.98).

Vitamin D analogues versus other treatments

For the outcome of IAGI/IGA, twice-daily calcipotriol was significantly more effective than coal tar polytherapy (SMD –0.59, 95% CI –0.87 to –0.31), and once-daily vitamin D analogue application was significantly less effective than a twice-daily application (SMD –0.24, 95% CI –0.38 to –0.09). No significant differences were observed between twice-daily application of calcipotriol and other comparators, including coal tar monotherapy, betamethasone dipropionate + salicylic acid, and topical tacrolimus.

Other comparative studies

A randomized, double-blind study compared calcipotriol with betamethasone valerate treatment over 6 weeks in 409 participants with psoriasis (*7*). Efficacy was assessed using the PASI at 2, 4 and 6 weeks. Reduction of PASI was statistically significant at all time points for both treatments, and there were no significant between-treatment differences. After 6 weeks of treatment, the mean PASI reduction was 5.50 for calcipotriol and 5.32 for betamethasone. Calcipotriol produced more local irritation.

Another study compared the safety and tolerability of calcipotriol cream with betamethasone 17-valerate cream in treating plaque-type psoriasis in a multicentre, double-blind, parallel-group study (*8*). The mean percentage reduction in PASI from baseline to end of treatment was 47.8% in the calcipotriol group and 45.4% in the betamethasone group. The reduction from baseline was highly significant in both groups, but the difference between the groups was not significant.

A study of 106 patients with chronic plaque psoriasis compared twice-daily calcipotriol with once-daily dithranol cream (short-contact regimen) (*9*). The mean percentage reduction in PASI from baseline to end of treatment was 57.0% in the calcipotriol group and 63.6% in the dithranol group, with no statistically significant difference between groups.

Efficacy of vitamin D analogues in children with psoriasis

A multicentre, prospective, open-label study evaluated the efficacy and safety of twice-daily topical calcipotriol for up to 8 weeks in 58 children with psoriasis (*10*). A statistically significant reduction in mean PASI scores was observed from the start to end of treatment. Marked improvement or clearance was reported in 65% of participants (investigator-assessed) and 62% of participants (patient-assessed). No significant alterations in serum ionized calcium levels or other biochemical or haematological parameters were seen over the course of treatment.

A multicentre, prospective, double-blind, parallel-group study evaluated the efficacy and safety of calcipotriol in 77 children (2–14 years old) with stable psoriasis involving less than 30% of the body surface (*11*). Participants were assigned to receive calcipotriol twice daily for 8 weeks or placebo. Both treatment groups showed significant improvement in PASI from baseline to the end of treatment, and the difference between the groups was not statistically significant. No serious adverse effects, in particular relating to calcium and bone metabolism, were reported.

Summary of evidence: harms (from the application)

Local skin irritation is estimated to occur in up to 20% of patients using topical vitamin D analogues. This is a clinical problem when treatment is applied to the face and therefore calcipotriol and other agents are not used for facial psoriasis.

Systemic hypercalcaemia has also been reported. Calcipotriol use has not been commonly associated with clinically significant hypercalcemia, possibly because it is rapidly metabolized after topical application. The cases where it has been recorded are generally single raised values in studies using vitamin D analogues over 52 weeks (*12–14*). A study involving hospitalized patients with severe and extensive psoriasis receiving up to 360 g of calcipotriol (50 micrograms/g) ointment a week found treatment did not affect bone turnover, but five out of 16 patients developed hypercalcaemia with a reduction in serum parathyroid hormone levels; this returned to normal within 2 days of stopping the treatment (*15*).

The above-mentioned Cochrane review analysed the adverse effects recorded in the included studies (*6*). Eleven studies evaluated local or systemic adverse events associated with calcipotriol, or both. The rate of withdrawal due to local adverse events ranged from 4% to 14%, and the rate of adverse events ranged from 20% to 41%. The larger trials reported higher adverse events rates (weighted mean: 36%). In a 52-week study, facial irritation affected 30% of participants in the early stages of the trial, but the incidence declined over time. The incidence of systemic adverse events was less common, with five out of eight studies reporting no significant effects.

Four studies evaluated both local and systemic adverse events associated with tacalcitol. The rate of withdrawal due to local adverse events ranged from 0% to 6%, and the rate of adverse events ranged from 10% to 21%. Three studies found no systemic adverse events. One study found that over half of participants with psoriasis affecting 10–20% of their body surface area exceeded the recommended daily dose of 5 g/day (up to 13 g daily). However, no effect on calcium homeostasis was reported. Systemic adverse events were identified in over half of participants in an uncontrolled study, but only 6/155 events were considered treatment-related.

Three studies evaluated adverse events associated with calcitriol. One study examined the tolerability and systemic adverse events of calcitriol used as monotherapy (3 micrograms/g ointment applied twice daily) in 253 patients. Three per cent of participants withdrew due to adverse events and 15% reported local adverse events. The rate of withdrawal due to systemic adverse events was low (0.4%), but four cases of hypercalcaemia were reported. The effects of high-dose calcitriol (15 micrograms/g once daily) were tested on three groups of participants, with the quantity used proportional to the area affected. No systemic adverse events, skin irritation, or clinically relevant changes in vital signs, haematology, biochemistry, urine or electrocardiogram were observed.

Studies on the use of calcipotriol in children reported low levels of local irritation in some children, but blood abnormalities, including those affecting calcium metabolism, were not observed (*10*, *11*, *16*).

Use in pregnancy

Adequate, well controlled studies of the use of calcipotriol during pregnancy are lacking. Fetal abnormalities have been reported in animal studies. It is recommended that calcipotriol be used during pregnancy only if the potential benefits justify the potential risks.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the management of psoriasis are not available.

Costs/cost–effectiveness

A cost–effectiveness study compared topical calcipotriol with short-contact dithranol in the treatment of mild to moderate plaque psoriasis (*17*). Only the costs of drug treatment to the British National Health Service were considered. Considering only drug treatment costs, calcipotriol was the more effective option and also the more costly. Over the long term, first-line treatment with calcipotriol had the highest expected cost per successful treatment at £ 164.91, compared with £ 126.25 with short-contact dithranol.

The reported listed costs for calcipotriol are: £ 7.43 (30 g) in the United Kingdom of Great Britain and Northern Ireland, US$ 149–263 (60 g) in the USA, Can$ 254–282 (60 g) in Canada and € 9.70 in Italy.

Availability

Calcipotriol is licensed for use in 97 countries worldwide.

Other considerations

The use of calcipotriol may spare the use of steroids. The application briefly described adverse events of topical corticosteroids, specifically tolerance, tachyphylaxis or diminishing therapeutic effect over time, as shown in eczema studies (*18*). The application also highlighted that in all environments, and particularly in warm and humid climates, misapplication of creams or ointments containing steroids to infections or infestations leads to suppression of inflammation and subsequent spread of the secondary infection (*19*,*20*), as well as allergic contact dermatitis accentuated by repeated use (*21*).

Committee recommendations

The Expert Committee noted that psoriasis is painful and disabling disease with a significant global burden and variable prevalence in different populations. The 2014 World Health Assembly resolution on psoriasis recognized the public health impact of psoriasis and the need for integrated management approaches. Severe forms of the disease are often treated using systemic therapies, but these can produce considerable toxicity and need careful monitoring. Topical treatment, such as calcipotriol, can be a valuable alternative, particularly for moderate disease.

The Committee noted that topical calcipotriol is more effective than placebo but not as effective as topical corticosteroids (e.g. betamethasone), a class of medicines that has been included in the EML since the first list was published. However, calcipotriol may be useful in patients who cannot tolerate corticosteroids or when toxicity associated with prolonged corticosteroid exposure becomes a problem. Calcipotriol has a favourable safety profile compared with topical corticosteroids due to low systemic absorption. It is easy to use, widely available and suitable for use in both adults and children.

The Expert Committee noted that, although there is limited evidence on the efficacy of calcipotriol for scalp psoriasis, it may be an appropriate alternative to prolonged topical use of corticosteroids on the scalp. Lotion formulations may provide greater patient acceptability for scalp application.

Therefore, the Expert Committee recommended the inclusion of calcipotriol on the core list of the EML and EMLc for the treatment of moderate forms of psoriasis.

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Section 15: DISINFECTANTS AND ANTISEPTICS

15.1 Antiseptics

15.2 Disinfectants

Hypochlorous acid – addition – EML and EMLc

Hypochlorous acid solution **ATC Code: N/A**

Proposal

Addition of hypochlorous acid solution to the core list of the EML and EMLc for use in disinfection, antisepsis and wound decontamination. Hypochlorous acid solutions are identified variously as electrolysed water, superoxidized water, acid electrolysed water, superoxidized saline and other variants.

Applicant

Briotech, Inc. Washington, DC, United States of America

WHO technical department

Not applicable.

EML/EMLc

EML and EMLc

Section

13 Dermatological medicines (topical)
15.1 Antiseptics
15.2 Disinfectants

Dose form(s) & strength(s)

Aqueous solution: 150 parts per million or greater of hypochlorous acid

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Hypochlorous acid solution and hydrogel were considered for inclusion on the Model Lists for use in wound management in 2017. The Expert Committee did not recommend addition on the basis of inadequate evidence, noting that the

quality of the evidence presented in the application for the solution formulation was uncertain, and that no evidence was presented for hydrogel (*1*).

Antiseptics currently included on the Model Lists are chlorhexidine, ethanol and povidone iodine. Disinfectants currently included are alcohol-based hand rub, chlorine base compound, chloroxylenol and glutaral.

Public health relevance (burden of disease)

Disinfection

The importance of environmental disinfection measures became more recognized in 2020 because of the coronavirus disease 2019 (COVID-19) pandemic. Regular decontamination of surfaces and air has become a necessary infection control measure.

Antisepsis and wound care

Infected wounds and the rise of antibiotic-resistant organisms are responsible for significant increases in morbidity, mortality and the cost of health care. Using topical antiseptics to treat superficial skin lesions with mild infections is advisable to avoid the use of antibiotics.

Summary of evidence: benefits (from the application)

Disinfection

An in vitro study showed antiprion activity of hypochlorous acid solution using intracerebral infectivity of treated prions of scrapie and with an in vitro fluorescent chemistry method showing efficacy against bovine spongiform encephalopathy, Creutzfeldt–Jakob disease and chronic wasting disease prions (*2*). Efficacy was shown to reach a log removal value of almost 6 after exposures of 60 minutes at room temperature. Log removal values of up to 3–4 were achieved with 5 minutes of contact with hypochlorous acid. Efficacy was also demonstrated against *Bacillus* spores.

A retrospective, single-institution cohort study evaluated the efficacy of universal skin decolonization using mupirocin and hypochlorous acid solution to decrease health care-associated methicillin-resistant *Staphylococcus aureus* (MRSA) infections in patients admitted to a burn intensive care unit in a tertiary-care community hospital (*3*). Global MRSA infection rates per 1000 patient days were 7.23 before the intervention and 2.37 after the intervention (incidence rate ratio 0.35, 95% confidence interval (CI) 0.17 to 0.65). Patients in the burn intensive care unit who did not receive universal decolonization had a 3.05 times higher risk of acquiring an MRSA infection than those who did. No complications were noted from the use of hypochlorous acid solution for skin decolonization.

An in vitro study to determine the efficacy of exposure to a pure hypochlorous acid solution for inactivation of high-risk human papillomavirus (HPV 16 and 18) found hypochlorous acid to be a highly effective disinfectant even with short contact times (*4*). All hypochlorous acid treatment times produced a > 99.99% reduction in infectivity of HPV16 and HPV18, comparable to the efficacy of 0.87% sodium hypochlorite.

Antisepsis

A randomized controlled trial in 111 participants on intraperitoneal dialysis evaluated the efficacy and safety of superoxidized solution versus povidone iodine following catheter placement in reducing the frequency of dialysis-associated infections (*5*). After 8 weeks of follow up, 24.5% of the povidone-iodine group had had catheter-related infections compared with 6.0% in the group treated with superoxidized solution ($P < 0.05$). In addition, the mean time for resolution of infection in the povidone-iodine group was 12 days compared with 4 days for the superoxidized solution group ($P < 0.05$).

An in vivo and in vitro study assessed the effectiveness of a hypochlorous acid-based wound cleanser compared with other cleansers (povidone-iodine and chlorhexidine) in disrupting MRSA and *Pseudomonas aeruginosa* biofilms. The study also evaluated the bioburden reduction of venous stasis wounds with the different cleansers (*6*). All agents tested significantly neutralized MRSA and *Pseudomonas aeruginosa* biofilms compared with saline control. Undiluted hypochlorous acid was significantly less cytotoxic than 1% and 10% povidone-iodine and chlorhexidine wound solution. No significant difference was found in bacterial reduction in wounds after treatment with hypochlorous acid for any type of bacteria examined. In wounds treated with hypochlorous acid or chlorhexidine, similar percentage reductions were seen in bacterial colony-forming units from precleansing levels when plated on tryptic soy agar, MacConkey agar, streptococcal agar and mannitol salt agar. Plates treated with chlorhexidine tended to have higher bacterial reduction on non-selective and Gram-negative agars, whereas plates treated with hypochlorous acid tended to have higher bacterial reduction in streptococcal-selective agars.

A randomized controlled trial of 80 participants with peritonitis compared peritoneal lavage with saline and peritoneal lavage with saline followed by superoxidized solution following surgery (*7*). Purulent discharge occurred in 20.0% of participants receiving superoxidized solution lavage versus 52.5% of participants receiving saline lavage ($P < 0.01$). The incidence of burst abdomen among the participants given superoxidized solution lavage was significantly lower than among the participants given saline lavage (12.5% versus 32.5%, $P < 0.05$). No difference in the incidence of superficial wound infection was observed between treatment groups.

A randomized trial of 178 participants compared the effectiveness of irrigation with neutral pH superoxidized solution and povidone iodine in reducing the incidence of sternotomy wound infection following coronary artery bypass graft surgery (*8*). Wound infection with sternotomy was reported in 5.7% of participants in the superoxidized solution group and 15.6% of participants in the povidone-iodine group ($P = 0.03$).

A randomized study of 100 participants undergoing exploratory laparotomy for peritonitis compared intraoperative peritoneal lavage with normal saline or normal saline followed by a superoxidized solution (*9*). Surgical site infection occurred in 14% of participants in the group treated with superoxidized solution compared with 40% of participants in the normal saline group ($P = 0.003$). The mean duration of hospital stay was similar between the two groups. Two participants in the superoxidized solution group died compared with eight participants in the saline group.

Wound care

A randomized trial of 60 participants evaluated the efficacy of hypochlorous acid versus povidone-iodine as a wound care agent in septic trauma wounds (*10*). Outcome measures for wound pain (no pain at day 14), odour (no odour at day 14), discharge (serous at day 14) and bacterial count (reduction in day 14 quantitative count) were significantly better in the hypochlorous acid group. At day 14, 90% of the participants treated with hypochlorous acid had wounds ready for surgical reconstruction, compared with 0% of the participants in the povidone-iodine group.

A randomized trial of 60 participants compared the efficacy of dressings with superoxidized solution and povidone-iodine in the management of infected diabetic ulcers (*11*). The mean change in ulcer area was significantly greater in participants treated with superoxidized solution dressings compared with participants given povidone-iodine dressings (2215 mm^2 versus 1641 mm^2, $P = 0.024$). Similarly, the mean percentage reduction in ulcer area in participants receiving superoxidized solution dressings was significantly greater (58.90% versus 40.90%; $P = 0.024$).

A randomized, prospective, multicentre, open-label pilot study tested the efficacy of topical superoxidized solution alone compared with normal saline irrigation plus oral levofloxacin, and superoxidized solution plus oral levofloxacin in 67 participants with mild diabetic foot infections (*12*). Based on the intention-to-treat population, the clinical success rate 14 days after completion of therapy (test of cure) for participants treated with superoxidized solution alone was 75.0%, compared with 72.0% for participants treated with superoxidized solution plus levofloxacin and 52.4% for participants treated with saline plus levofloxacin. Differences in clinical success rates were not statistically significant.

A randomized case control trial of 100 patients with a variety of wounds compared the efficacy and outcomes of superoxidized solution-saturated dressings and povidone-iodine saturated dressings (*13*). The most common infecting organism isolated was *Pseudomonas aeruginosa*, followed by *Staphylococcus aureus* and *Klebsiella* spp. The decrease in surface area of wounds at the end of 1, 2, 3 and 4 weeks was significantly greater in the superoxidized solution group ($P = 0.005$, $P = 0.002$, $P < 0.001$ and $P < 0.001$, respectively).

A randomized controlled trial examined the efficacy and safety of a superoxidized solution compared with povidone-iodine (as adjuncts to systemic antibiotics and debridement as needed) in the management of wide (> 5 cm) postsurgical lesions of the diabetic foot in 40 participants (*14*). Healing, as measured by complete re-epithelization, occurred in 90% of the participants treated with superoxidized solution compared with 55% of the povidone-iodine group ($P < 0.01$). Participants treated with superoxidized solution also had fewer episodes of reinfection ($P < 0.01$).

A retrospective analysis of 897 patients with 1249 venous leg ulcers treated with hypochlorous acid solution found that all venous leg ulcers healed completely. Treatment involved cleaning and debriding foreign matter, debris and necrotic material by application of hypochlorous acid solution, with or without pressure and abrasion, using a sterile gauze soaked with hypochlorous acid. Sharp debridement was performed where required within 10 days of presentation. All ulcers were dressed and/or loosely packed with sterile gauze soaked with hypochlorous acid. Compressive bandaging was applied. Light abrasion using sterile gauze and flushing with hypochlorous acid solution was performed every few days. The longest healing times were observed in 10 patients for whom compression therapy was contraindicated. However, aggressive management adding hypochlorous acid resulted in complete wound closure within 180 days in these 10 patients (*15*).

A randomized, single-blind trial studied the outcomes of standard care (without neutral pH superoxidized solution) and standard care plus neutral pH superoxidized solution in the treatment of 45 patients with diabetic foot ulcers (*16*). Odour reduction was reported in 100% of participants treated with superoxidized solution compared with 20% in the standard care group. Surrounding cellulitis diminished in 80.5% of participants treated with superoxidized solution versus 43.7% in the standard care group and advancement to granulating tissue stage occurred in 90.4% versus 62.5%.

A hundred patients with diabetic foot ulcer wounds were randomized to treatment with either daily superoxidized solution or saline-soaked gauzes (*17*). Participants treated with hypochlorous acid had a significantly shorter period of hospitalization than saline-treated participants (68% versus 20% stayed in hospital for 1–7 days, $P < 0.05$) and a greater proportion experienced a downgrading of wound category (62% versus 15%, $P < 0.05$).

Two hundred patients with different types of wounds were prospectively randomized to treatment with either superoxidized solution or povidone-iodine (using saturated gauzes), and antibiotics (*18*). After a mean follow-up of 21 days, the average reduction in the wound size of diabetic foot ulcer in the group treated with superoxidized solution was 70% compared with 50% in the povidone-iodine group. Earlier granulation and epithelization were also seen for wounds treated with superoxidized solution compared with those treated with povidone-iodine (100% versus 85% at day 18).

Summary of evidence: harms (from the application)

Clinical adverse events from exposure to pure hypochlorous acid (present at a pH between 4.0 and 5.33) have not been recorded in the medical literature. Adverse events have been reported following exposure to relatively high pH (> 6.5), crude formulations containing mixed oxidants, including hypochlorite, which result from poorly controlled manufacturing processes.

Eye and skin inflammation and respiratory irritation are common with hypochlorite (bleach), which can be present at levels of 30% or more in hypochlorous acid solutions made or adjusted to pH 7, or in swimming pools that are improperly managed, allowing the pH to rise into the alkaline range.

A 2011 study evaluated the risk of biological toxicity in a mouse model when acid-electrolysed water was ingested as drinking water for 8 weeks. No abnormal findings were observed and the authors concluded this water would be safe if used as a mouthwash, even if ingested (*19*).

Another study using an animal model looked at the potential toxicity associated with infusions of superoxidized solution into the intraperitoneal cavity of rats. No significant differences in blood biochemistry, renal function or liver function were found between rats infused with hypochlorous acid and control rats (*20*).

A review of acid-electrolysed water versus normal saline as a peritoneal lavage to prevent postsurgical infections after perforated appendicitis in children found no evidence of toxicity associated with acid-electrolysed water (*21*).

Environmental safety

Hypochlorous acid is a highly reactive molecule and short-lived when exposed to pathogens or other biological matter. On exposure, pure hypochlorous acid degrades within minutes to form sodium chloride and water, becoming benign and non-reactive saltwater closely analogous to human tears (*22*). Because of that rapid reactivity, pure hypochlorous acid at a label concentration of 180 parts per million poses no risk of environmental contamination (except as a mild 0.9% salt solution) and does not require personal protective equipment. It can be stored without any hazardous materials protocol and can be disposed of with no risk of generating a toxic waste stream.

In contrast, impure hypochlorous acid/hypochlorite solutions, such as hypochlorite (bleach), require personal protective equipment and hazardous material storage, and must be disposed of as both a toxic materials risk and an environmental hazard. These hazard considerations also apply to other classes of antisepsis and disinfection agents.

Additional evidence (not in the application)

Not applicable

WHO guidelines

The WHO interim guidance document on cleaning and disinfecting surfaces in relation to COVID-19 specifies that "hypochlorite-based products include liquid (sodium hypochlorite), solid or powdered (calcium hypochlorite) formulations. These formulations dissolve in water to create a dilute aqueous chlorine solution in which undissociated hypochlorous acid (HOCl) is active as the antimicrobial compound" (*23*).

Costs/cost–effectiveness

The application states that modern manufacturing permits the generation of pure, stable hypochlorous acid in large volumes for roughly one eighth the cost of previous methods. Current pricing pf hypochlorous acid produced at scale can now be less than US$ 2 per wholesale litre at the manufacturing facility, with small regional variations.

Availability

Multiple branded aqueous hypochlorous acid formulations have been approved for topical use in wound management by the US Food and Drug Administration. The Food and Drug Administration has also approved hypochlorous acid for strong disinfection and sterilization of medical instruments (*24*). Multiple branded hypochlorous acid products are approved as COVID-19 disinfectants.

A class III medical product approval for hypochlorous acid has been granted in the European Union, and the Japanese Ministry of Health has approved the use of hypochlorous acid for topical medical applications.

The capacity to produce hypochlorous acid from small, local and networked manufacturing facilities is available. This eliminates the cost of transportation and allows remote locations to produce pure and stable hypochlorous acid that meets quality standards.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that recommendations for chlorine-based products, including hypochlorite formulations, are included in the 2020 WHO guidance on cleaning and disinfection of environmental surfaces in the context of COVID-19. Liquid, solid or powered hypochlorite-based formulations dissolve in water to create a dilute aqueous chlorine solution in which undissociated hypochlorous acid is the active antimicrobial compound. The EML and EMLc currently list chlorine-based compounds, with a square box, intended to indicate that various formulations can be acceptable alternatives for selection and use. However, the current listing does not specify the alternative formulations.

In the review of square box listings on the Model Lists considered at the current meeting, an amendment to the square box listing of chlorine-based compounds in the disinfectant section of the EML and EMLc was proposed. The Committee recommended that the listing should be amended to specify the different recommended formulations to provide greater clarity and guidance for countries. This recommendation will result in liquid and solid formulations of chlorine-based compounds being specifically included as alternatives. Therefore, the Committee considered that a separate listing for the proposed formulation of hypochlorous acid solution was not necessary.

As regards antiseptic use, the Committee noted that hypochlorous acid appears to be a safe and effective antiseptic with a broad activity against a wide range of pathogens and has an acceptable safety profile. Recent advances in manufacturing have improved standardization of the product. However, the evidence supporting these considerations is relatively limited and derived from small and heterogeneous studies. The Expert Committee noted that ongoing studies will have the potential to better clarify the advantages of hypochlorous acid and would inform a future consideration of this product for inclusion on the Model Lists.

Therefore, the Expert Committee did not recommend hypochlorous acid for inclusion in the EML and EMLc for antisepsis and wound decontamination at this time, but advised that it would welcome a future application including data from ongoing studies and a more comprehensive review of the literature.

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Section 18: MEDICINES FOR ENDOCRINE DISORDERS

Simvastatin – new indication – EML

Simvastatin **ATC Code: C10AA01**

Proposal

Extension of the indications for simvastatin on the EML to include treatment of polycystic ovary syndrome in women.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EML

Section

18 Medicines for endocrine disorders

Dose form(s) & strength(s)

Tablet: 20 mg

Core/complementary

Core

Individual/square box listing

Individual

The application noted that current evidence does not confirm that there is a true pharmacological class effect for statins in polycystic ovary syndrome. In addition, statins have a pharmacological variation that might plausibly suggest different outcomes with polycystic ovary syndrome.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Simvastatin was added to the EML in 2007 for the secondary prevention of cardiovascular disease in high-risk populations with a square box listing giving

pravastatin, lovastatin, fluvastatin and atorvastatin as possible alternatives, with the choice to be made at the national level. The Committee acknowledged that there was high-quality clinical evidence from many large randomized trials and systematic reviews that established the clinical benefits of statins, in conjunction with lifestyle modification, for this indication (*1*).

Simvastatin has not previously been considered by the Expert Committee for use in the treatment of polycystic ovary syndrome.

Generally, polycystic ovary syndrome presents as a spectrum of heterogeneous disorders of reproduction and metabolism in women with frequent symptoms, such as abnormal menstruation, infertility, obesity, hirsutism, acanthosis nigricans, acne and ovarian cysts. Expert groups commonly recommend using the Rotterdam criteria for diagnosis of polycystic ovary syndrome (*2*, *3*). The Rotterdam criteria require that the patient exhibits two of three of the following characteristics: oligo- and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; and/or ultrasound evidence of polycystic ovaries (*4*).

Public health relevance (burden of disease)

Polycystic ovary syndrome is the most common endocrinopathy affecting women of reproductive age globally, with a prevalence of about 8–13% (*5*). Due to discrepancies between diagnostic criteria and symptom presentation, the prevalence may be as high as 20% (*6*). The prevalence and disease presentation vary widely by ethnicity and geographical location (*7*, *8*).

Polycystic ovary syndrome is a leading cause of infertility. Furthermore, women with polycystic ovary syndrome are at a higher risk of developing impaired glucose tolerance, type 2 diabetes, cardiovascular disease, hypertension, metabolic syndrome and certain gynaecological cancers (*5*, *9*). Women with polycystic ovary syndrome have a substantially lower quality of life compared with control groups and population data (*10*).

Visible signs of excess androgens (such as hirsutism, acne and alopecia) have noticeable effects on physical appearance that can affect neuropsychological status. Obesity also has an important psychosocial effect (*11*). Women, especially adolescents, with polycystic ovary syndrome are at increased risk of anxiety and depression (*12–14*).

Associations between socioeconomic status and polycystic ovary syndrome prevalence vary; however, women of low socioeconomic status during adulthood, or low socioeconomic status during childhood but high personally attained socioeconomic status during adulthood, are more likely to have polycystic ovary syndrome (*13*, *15*).

Summary of evidence: benefits (from the application)

Systematic reviews and meta-analyses

Five systematic reviews and meta-analyses were identified that included an evaluation of simvastatin for the management of polycystic ovary syndrome (*16–20*). Variation in inclusion criteria (e.g. any statin), search approach, analytical techniques and outcomes of interest produced variability in conclusions on the usefulness of simvastatin and other statins for this indication. Three reviews focused on the evaluation of pharmacological class (*16*, *19*, *20*), and concluded simvastatin may provide some benefit with regard to biochemical markers such as lipid and testosterone levels. Two reviews included a comparison of atorvastatin, simvastatin and rosuvastatin and found atorvastatin to be superior in terms of effects on testosterone or dehydroepiandrosterone levels. However, small sample sizes limit the clinical usefulness of these findings (*17*, *18*). Further studies are needed to assess clinical outcomes.

Randomized clinical trials

Fifteen randomized controlled trials compared the effectiveness of regimens containing simvastatin with one or two other treatment options. Most trials had small sample sizes. Trial data indicated positive effects of simvastatin therapy on lipids, hormone levels and other measures of disease activity in women with polycystic ovary syndrome.

Two trials compared simvastatin with placebo. A trial in 61 women with polycystic ovary syndrome pursuing in vitro fertilization found positive effects on testosterone and cholesterol but did not find benefit in terms of fertilization success (*21*). Another trial in 200 women with polycystic ovary syndrome found positive effects of simvastatin compared with placebo on hormone levels, lipids, menstrual regularity, hirsutism, acne, ovarian volume, body mass index and waist-to-hip ratio, but did not on fasting glucose, fasting insulin or measures of insulin resistance (*22*).

Two trials compared simvastatin with metformin in women with polycystic ovary syndrome (*23*, *24*). One trial included 400 women and found simvastatin was superior to metformin in improving total cholesterol, low-density lipoprotein, C-reactive protein and acne; metformin was superior in improving fasting blood sugar and insulin measures (*23*). The second trial included 40 women with polycystic ovary syndrome pursuing in vitro fertilization; both regimens were associated with beneficial effects on biochemical parameters, but neither regimen affected fertilization outcomes (*24*).

Three trials with a total of 401 women with polycystic ovary syndrome compared simvastatin, metformin and the combination of simvastatin and metformin (*25–28*). In one of the trials, neither metformin nor simvastatin were found to affect levels of free fatty acid binding protein-4 or retinol binding

protein-4, known to contribute to metabolic syndrome (*26*). In another trial, women treated with simvastatin had significantly better responses than women treated with metformin alone for outcomes including number of spontaneous menses in 6 months, ovulation, ovarian volume, body mass index, waist-to-hip ratio, hirsutism score, acne, total and free testosterone, and other metabolic parameters (*25*). In the third trial, no significant differences were found between treatment groups for reduction in total testosterone, reduction in body mass index, or improvements in markers of systemic inflammation and endothelial function. Simvastatin treatment was superior to metformin alone (*27*, *28*).

One trial compared simvastatin, metformin and flutamide plus oral contraceptives in 102 women with polycystic ovary syndrome and metabolic syndrome (*29*). After 6 months, simvastatin was superior to the other two regimens for reductions in waist circumference, body mass index and triglyceride levels. Metformin was superior to the other regimens for effects on fasting blood sugar.

Two trials compared simvastatin to atorvastatin in 116 women with polycystic ovary syndrome (*30*, *31*). Both trials found the statin regimens lead to improvements in lipid levels and other measures of disease activity, while benefits attributed to the individual agents varied to some extent; the data suggest possible greater effects of simvastatin on hormone levels, while atorvastatin may have a greater effect on measures of insulin resistance.

Two trials evaluated simvastatin plus metformin versus metformin alone in 192 women with polycystic ovary syndrome (*32*, *33*). Both trials found the regimen containing simvastatin-led to greater improvements in hormone levels (e.g. testosterone, follicle stimulating hormone and luteinizing hormone) and lipids.

One trial evaluated simvastatin plus oral contraceptives versus oral contraceptives alone in 48 women with polycystic ovary syndrome (*34*). The combination regimen significantly reduced serum testosterone, other hormone levels (e.g. follicle stimulating hormone and luteinizing hormone), reduced total cholesterol and low-density lipoprotein levels, and increased high-density lipoprotein levels. The hirsutism score was also slightly reduced.

Summary of evidence: harms (from the application)

The safety and tolerability profile of simvastatin as a treatment for hyperlipidaemia is well known. The literature describing the use of simvastatin or atorvastatin in the treatment of women with polycystic ovary syndrome indicates a safety profile comparable to that observed in the substantial evidence on statin use for hyperlipidaemia.

Simvastatin is contraindicated in pregnancy and breastfeeding. It should only be used in women of childbearing potential when they are highly unlikely to conceive.

Additional evidence (not in the application)

Comments were received from Dr Barbara Stegmann, Clinical Lead for Women's Health, Organon & Co. (marketing authorization holder for Zocor brand of simvastatin), highlighting concerns about the of use of statins (including simvastatin) during pregnancy and in women of childbearing potential, including a category X designation by the United States Food and Drug Administration for use in pregnancy (drugs that can cause birth defects and developmental abnormalities in humans), and the contraindications for use during pregnancy and breastfeeding issued by the Food and Drug Admiration, European Medicines Agency and other regulatory agencies (*35–37*).

WHO guidelines

WHO guidelines for the treatment of women with polycystic ovary syndrome are not currently available.

Costs/cost–effectiveness

No cost–effectiveness data were presented in the application.

Simvastatin is widely used globally and is generally affordable.

A national cost analysis using United States data, noted that the estimated annual national health care cost associated with polycystic ovary syndrome was US$ 1.16 billion, with the greatest contributors being treatment for diabetes, oral contraceptives, initial evaluation, medical costs associated with obesity, and infertility treatment (*38*). An analysis from the United Kingdom of Great Britain and Northern Ireland focused on the costs associated with diabetes in women with polycystic ovary syndrome, and estimated the annual health care burden of the condition was at least £ 237 million (*39*).

Availability

Simvastatin is widely available globally in branded and generic forms. Currently, it does not have regulatory approval for the treatment of polycystic ovary syndrome.

Other considerations

The applicants reviewed data from a phenome-wide association study. Such studies can identify diseases or conditions (phenotypes) that are associated with a specific gene or genetic variant (*40*). Phenome-wide association studies make use of existing data from the ExomeChip genotyping platform (about 250 000 coding variants across the protein coding region of the genome) and electronic health records of about 35 000 patients. Because the rationale of phenome-wide association studies can be extended to predict phenotypic manifestations of pharmacological targeting (such as with simvastatin) of a given gene product

in humans, these methods are used for drug repurposing (*41*). As a hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin reduces cholesterol. The phenotypes associated with the missense single nucleotide polymorphism (SNP) (Ile638Val) in the HMGCR gene are risk-causing, so in this regard, the SNP is functioning as an HMG-CoA reductase activator (the opposite of the drug). This SNP is associated with increased risk of cholesterol disorders, and is also associated with oophorectomy and ovarian cysts. The applicants assert this evidence supports the proposal to treat polycystic ovary syndrome with simvastatin.

Committee recommendations

The Expert Committee noted that polycystic ovary syndrome is a frequent disease in women worldwide. It is associated with infertility, obesity, metabolic syndrome, hypertension, type 2 diabetes, cardiovascular disease and some gynaecological cancers, and has important psychosocial effects, highlighting the need for appropriate treatment.

The Committee also acknowledged that repurposing of old drugs for new indication is important and should be further investigated. However, the available evidence shows that while simvastatin can improve biochemical markers in patients with polycystic ovary syndrome, there is no evidence that these improvements result in better clinical outcomes. Moreover, the evidence seems to suggest statins may differ with regard to their effect on surrogate markers, such as hormone levels, with atorvastatin possibly being superior to simvastatin.

The Committed noted that simvastatin should not be used in pregnancy as studies in animals and humans have shown fetal abnormalities or the risk of human fetal abnormalities. This an important issue as polycystic ovary syndrome mainly affects women of reproductive age and one aim of treatment of polycystic ovary syndrome is to improve fertility.

Therefore, the Expert Committee did not recommend the addition of simvastatin for polycystic ovary syndrome due to an absence of evidence for clinical benefits.

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18.5 Medicines for diabetes

18.5.1 Insulins

Long-acting insulin analogues – addition – EML and EMLc

Insulin degludec	**ATC Code: A01AE06**
Insulin detemir	**ATC Code: A01AE05**
Insulin glargine	**ATC Code: A10AE04**

Proposal

Addition of long-acting insulin analogues (insulin degludec, insulin detemir and insulin glargine) to the core list of the EML and EMLc for treatment of type 1 and type 2 diabetes mellitus.

Applicant

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WHO technical department

Management of noncommunicable diseases

EML/EMLc

EML and EMLc

Section

18.5.1 Insulins

Dose form(s) & strength(s)

Injection: 100 IU/mL in 3 mL cartridge or prefilled pen

Core/complementary

Core

Individual/square box listing

Square box listing, incorporating insulin glargine, insulin degludec and insulin detemir and biosimilars.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Long-acting insulin analogues were previously considered by the Expert Committee in 2013, 2017 and 2019 (*1*–*3*).

Insulin analogues are medicines whose molecular structure is similar to endogenous human insulin, a 51-amino acid polypeptide. Human insulin is available in various forms, as (regular) insulin with a rapid onset of action, slow-acting neutral protamine Hagedorn (NPH) insulin or zinc-based preparations.

Insulin analogues were designed to mimic physiological insulin profiles more closely than human insulin injections, which is relevant especially for people with type 1 diabetes who are more at risk of frequent and severe hypoglycaemia events. Insulin analogues can be classified based on their duration of action. The long-acting insulin analogues insulin glargine and insulin degludec were designed to provide more stable basal insulin-action profiles and longer coverage of insulin needs. These medicines are typically dosed once daily, but detemir may be dosed twice daily in some circumstances. The ultra-long-acting insulin degludec has a duration of action that lasts up to 42 hours and is dosed once daily as basal insulin.

In 2017, the Expert Committee noted that the magnitude of the benefit provided by long-acting insulin analogues was not large compared with human insulin. The Committee considered that the benefits of long-acting insulin analogues over human insulin in reduced glycated haemoglobin and reduced hypoglycaemia were modest and did not justify the current large difference in price between long-acting insulin analogues and human insulin (*2*).

In 2019, the Committee again did not recommend the addition of long-acting insulin analogues to the Model List, reiterating the conclusion of the 2017 Committee. The Committee was still concerned about the ongoing problems of access and affordability of insulin worldwide, despite human insulin not being patented. The Committee noted the long-standing domination of the insulin market by three manufacturers, limiting broader competition and slowing the entry of biosimilars to the market. The Committee also recommended WHO coordinate a series of actions to address the issues of insulin access and affordability (*3*).

Public health relevance (burden of disease)

Worldwide, diabetes affected an estimated 463 million people in 2019 (9.3% of the global population), of whom 79% live in low- and middle-income countries (*4*). The number of people with diabetes has almost tripled in the past 3 decades

due to: increase in population size; population ageing; and the increasing prevalence of the main risk factors for diabetes – overweight, obesity and physical inactivity (*5*). In 2019, diabetes was responsible for over 1.5 million deaths and 2.79% of all global disability-adjusted life years (*6*). The burden of diabetes is projected to increase to affect 700 million people in 2045 (*7*).

Diabetes is estimated to reduce life expectancy by 6 years when diagnosed at 40 years (*8*), and is a major cause of peripheral neuropathy, blindness, kidney failure and lower limb amputation. Diabetes complications affect quality of life and often lead to premature deaths, which is experienced by about a half of all people with diabetes.

The incidence and prevalence of type 2 diabetes are much higher than type 1 diabetes, with type 2 diabetes responsible for about 90–95% of all diabetes cases (*4*). The annual global expenditure on health care for people with diabetes is estimated to be US$ 850 billion, 12% of the overall global health care expenditure (*7*).

All people with type 1 diabetes have an absolute need for insulin for survival. A proportion of people with type 2 diabetes (less than 10%) also need insulin at some point in the course of their disease (*9*).

Summary of evidence: benefits and harms (from the application)

Type 1 diabetes

A 2018 meta-analysis including 28 randomized controlled trials found that, compared with human NPH insulin (an insulin with intermediate duration of action), long-acting insulin analogues led to a significant reduction in general hypoglycaemia (relative risk (RR) 0.95, 95% confidence interval (CI) 0.91 to 0.99), nocturnal hypoglycaemia episodes (RR 0.66, 95% CI 0.57 to 0.76) and haemoglobin A1c (HbA1c) – mean difference (MD) –0.17, 95% CI –0.23 to –0.12. No significant difference was observed for severe hypoglycaemia (RR 0.94, 95% CI 0.71 to 1.24) (*10*).

A 2021 systematic review and network meta-analysis of 64 randomized controlled trials and one non-randomized controlled trial compared long-acting insulin analogues and biosimilars with human insulin in adults with type 1 diabetes (*11*). The risk of bias varied for different elements (unclear in most trials for the random sequence generation, allocation concealment and selective reporting; high in most trials for the blinding of participants and personnel and other biases). The network meta-analysis found that long-acting insulin analogues led to fewer major or serious hypoglycaemia episodes (odds ratio (OR) 0.63, 95% CI 0.51 to 0.79) and nocturnal hypoglycaemia episodes (OR 0.74, 95% CI 0.58 to 0.94), and reductions in HbA1c (MD –0.14 percentage points (95% CI –0.22 to –0.06), fasting plasma glucose (MD –1.03 mmol/L (95% CI –1.33 to –0.73 mmol/L) and weight (MD –0.7 kg (95% CI –1.08 to –0.32 kg).

No significant differences were found for all-cause hypoglycaemia, vascular complications, microvascular complications, macrovascular complications, any adverse events, serious adverse events and drop-outs due to adverse events (*11*). A systematic review of eight studies (four randomized controlled trials and four cohort studies) evaluated quality of life outcomes with insulin glargine compared with human NPH insulin (*12*). Five studies reported statistically significant differences in quality of life, favouring glargine over NPH insulin, in certain areas. One study did not report on quality of life outcomes, and two reported no statistically significant difference in any of the variables measured. Where insulin glargine was significantly better in quality of life measures, differences were in the areas of satisfaction with treatment or perception of hyperglycaemia.

A systematic review of severe hypoglycaemia in paediatric patients with type 1 diabetes, including two real-world observational studies, compared long-acting insulin analogues and human NPH insulin and had inconclusive findings (*13*). The review noted a temporal trend showing marked reduction in the incidence of severe hypoglycaemia since 1993, which the authors proposed could be associated with increased use of new insulin therapies and related devices and diagnostics. One of the included analyses of 2025 patients found a significantly lower incidence rate ratio of 0.46 (95% CI 0.22 to 0.95) for serious hypoglycaemia with long-acting insulin analogues compared with NPH insulin (*14*). In another analysis (7266 patients), hypoglycaemia episodes were significantly more common in patients using long-acting insulin analogues than in patients using NPH insulin (OR 1.57, 95% CI 1.21 to 2.03). These episodes included situations that required attention to prevent glucose levels dropping further and situations in which children experienced some impaired awareness. The increased risk for severe hypoglycaemia episodes requiring external assistance was not statistically significant (OR 1.42, 95% CI 0.86 to 2.35) (*15*).

A Cochrane systematic review comparing long-term treatment with (ultra-)long-acting insulin analogues with NPH insulin included 26 randomized controlled trials in adults and children (8784 participants) which had a follow-up duration of at least 24 week (*16*). Insulin detemir was associated with a significantly lower risk of severe hypoglycaemia events than NPH insulin (RR 0.69, 95% CI 0.52 to 0.92 (eight studies, 3219 participants; moderate-certainty evidence)). No significant difference was found between insulin glargine and NPH insulin in their effect on severe hypoglycaemia events (RR 0.84, 95% CI 0.67 to 1.04 (nine studies, 2350 participants; moderate-certainty evidence)). The review did not explore a pharmacological class effect for long-acting analogues, and combined results across detemir trials and glargine trials. Results were uncertain for severe nocturnal hypoglycaemia for both detemir and glargine. Few data were available on mortality and other important outcomes for patients. The meta-analysis found no significant difference in HbA1c between insulin

detemir and NPH insulin (MD 0.01%, 95% CI –0.1 to 0.1% (eight studies, 3122 participants; moderate-certainty evidence)), or between insulin glargine and NPH insulin (MD 0.02%, 95% –0.1 to 0.1% (nine studies; 2285 participants)).

Type 2 diabetes

A 2020 Cochrane review comparing (ultra-)long-acting insulin analogues with NPH insulin included 24 randomized controlled trials in adults with type 2 diabetes. The review found a significant reduction in certain measures of hypoglycaemia for insulin glargine or insulin detemir compared with NPH insulin, but no significant differences in severe hypoglycaemia events, HbA1c, all-cause mortality, diabetes-related complications, or adverse events other than hypoglycaemia (*17*). The review did not explore a pharmacological class effect for long-acting analogues, and combined results across detemir trials and glargine trials. For health-related quality of life, three trials reported no statistically significant difference between insulin glargine and NPH insulin. The other three trials reported no statistically significant difference between insulin detemir and NPH insulin. The authors noted that, overall, the included studies used very low blood glucose/HbA1c target values; the findings may therefore be less applicable for patient groups where less aggressive glycaemic targets are used (e.g. elderly people).

Pooled analysis of type 1 and 2 diabetes

A 2015 systematic review of 76 observational studies evaluated the risk of severe hypoglycaemia in patients with type 1 and 2 diabetes as observed in everyday clinical practice for various drug regimens (*18*). In type 1 diabetes, the estimated annual probability of one or more severe hypoglycaemia event per patient varied from 21.4% (95% CI 11.3% to 43.0%) for basal-bolus routine with insulin analogues to 33.8% (95% CI 17.9% to 67.5%) for basal-bolus routine with human insulin. Differences for type 2 diabetes were more pronounced: the estimated annual probability of one or more severe hypoglycaemia event per patient varied from 4.8% (95% CI 1.2% to 27.0%) for basal-bolus routine with insulin analogues to 33.8% (95% CI 17.9% to 67.5%) for basal-bolus routine with human insulin. Differences were minimal when basal therapy was combined with oral antidiabetic medication.

Another systematic review and meta-analysis of 23 studies compared insulin analogues with human insulins in hospitalized adults with type 1 or 2 diabetes. Outcomes included hyperglycaemia episodes, surgical site infection, postoperative complications, length of hospital stay and mortality (*19*). Comparing analogue basal-bolus routine regimens with human insulin basal-bolus regimens, a meta-analysis of four randomized trials estimated that analogues reduced days spent in hospital by 0.9 days (95% CI −1.45 to −0.34

days), with low quality of evidence. One randomized controlled trial found lower rates of postoperative complications (RR 0.69, 95% CI 0.52 to 0.93) with very low quality of evidence. Two randomized controlled trials and one cohort study compared long-acting insulin analogues with human NPH insulin in hospitalized patients. The cohort study (in 172 hospitalized patients undergoing major surgery) found a reduction in hypoglycaemia events (very low-quality evidence), while the randomized trials were inconclusive.

A 2015 systematic review identified eight observational studies comparing insulin glargine with NPH insulin, and one observational study and one randomized controlled trial comparing insulin detemir with NPH insulin in patients with (pre-)gestational diabetes (*20*). A meta-analysis of these studies found no significant differences in fetal, neonatal or maternal outcomes. Similarly, a meta-analysis found no significant differences in fetal/neonatal or maternal outcomes for insulin detemir.

With regard to biosimilars, evidence to date indicates no safety signals when switching patients from originator to biosimilar insulin (*21*).

Additional evidence (not in the application)

Some authors have studied the potential risk of developing different types of cancer with medicines used to manage diabetes, including long-acting insulin analogues.

A 2013 systematic review and meta-analysis evaluated the cancer risk associated with insulin use from experimental and observational studies (*22*). Insulin exposure was found to be associated with an increased risk of cancer in the pancreas (RR 2.58, 95% CI 2.05 to 3.25), liver (RR 1.84, 95% CI 1.32 to 2.58), kidney (RR 1.38, 95% CI 1.06 to 1.79), stomach (RR 1.65, 95% CI 1.02 to 2.68) and respiratory system (RR 1.30, 95% CI 1.14 to 1.47), and decreased risk of prostate cancer (RR 0.80, 95% CI 0.73 to 0.88). Insulin glargine exposure was associated with a decreased risk of colon cancer (RR 0.71, 95% CI 0.56 to 0.91) and a marginally significant increased risk of breast cancer (RR 1.14, 95% CI 1.01 to 1.29) compared with users of non-glargine insulin. The results from individual studies were very variable and for most cancers there were few cases, calling into question the certainty of the findings.

Two meta-analyses of data from randomized controlled trials from manufacturer's pharmacovigilance databases evaluated the role of insulin in the generation of cancers. When insulin glargine was compared with any active comparator (insulin or oral antidiabetics), there were slightly fewer cancer cases in the glargine arm but the difference was not statistically significant (RR 0.90, 95% CI 0.60 to 1.36) (*23*). The second meta-analysis compared insulin detemir with NPH insulin and found more cases of cancer in the NPH insulin arm (OR 2.44 95% CI 1.01 to 5.89) (*24*).

WHO guidelines

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes (*25*) include the following recommendations.

- Use human insulin to control blood glucose levels in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence).
- Consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycaemia).

The second recommendation is weak, "reflecting the lack of, or very low-quality evidence for, any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin"

Costs/cost–effectiveness

There are long-standing concerns about the prices of long-acting insulin analogues, which are substantially higher than prices of human insulins in most comparisons. This is of particular concern given the broader crisis in global access to insulin therapy in general, where an estimated one in two people who need insulin cannot afford it (*26*). The application notes that the price reductions for analogue insulins and biosimilars has fallen since the 2019 application.

Most available cost–effectiveness studies focus on high-income settings. In all studies, procurement costs for long-acting insulin analogues are considerably greater than for human insulins. Some cost–effectiveness analyses have found that, despite greater procurement cost, insulin analogues are more cost-effective than human insulins because of savings resulting from (assumed/modelled) health benefits such as lower rates of hypoglycaemia.

A systematic review of the cost–effectiveness of insulin analogue included 50 studies, of which 33 focused on type 2 diabetes, 11 on type 1 diabetes, and six on both type 1 and type 2 diabetes (*27*). Twenty-one studies compared long-acting insulin analogues with NPH insulin, all of which were from high-income countries. Long-acting insulin analogues were dominant over NPH insulin in five comparisons (i.e. had both lower cost and greater benefits) and were dominated by NPH in one comparison (i.e. had both greater cost and lesser benefits). Apart from these cases, the incremental cost–effectiveness ratios for long-acting insulin analogues compared to insulin NPH ranged from US$ 661 to US$ 361 721 per quality adjusted life year (QALY). This large range in the incremental cost–effectiveness ratios is caused by

different underlying assumptions used across studies, particularly regarding: (i) the baseline characteristics of patients, complication frequency and severity, use and cost of self-monitoring blood glucose test strips and devices (e.g. pen, cartridge, vial), and (ii) the different (estimated) magnitudes of benefit in reducing hypoglycaemia events and reductions in HbA1c.

Six cost–effectiveness studies of long-acting insulin analogues published between 2015 and 2020 were identified in the application (*28–33*). Long-acting insulin analogues were found to be cost-effective compared to human insulins in several studies in Asia. In France, insulin glargine was cost–effective but not insulin detemir. Neither was cost-effective in a study within the Brazilian health system. A study in China assessed insulin cost in wages and found that a month's supply of long-acting insulin analogues cost 14–16 days' wages for the lowest-paid government worker compared with 4–7 days for other insulins.

In their most recent report (2017), the Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) study gave insulin prices from a range of sources, including: government procurement prices in 26 countries, the Gulf Cooperation Council and the United Nations Relief and Works Agency for Palestine Refugees; prices paid by patients (solicited from respondents in 43 countries); and reimbursement prices collected from publicly accessible databases for 28 countries (*34*). For government procurement, the median price for 1000 units of long-acting insulin analogues was US$ 34.20 compared with US$ 5.99 for human insulin. When bought by patients from public-sector facilities, the median price of 1000 units for long-acting insulin analogues was US$ 45.03 compared with US$ 7.64 for human insulin. When bought by patients in the private sector, the median price for long-acting insulin analogues was US$ 39.35 compared with US$ 16.65 for human insulin.

A report on recent trends in insulin prices submitted to the 2021 Expert Committee highlighted that in many countries, access to long-acting insulin analogues is limited and hampered by the higher costs compared with human insulin (*35*). The report states that "Overall, there is great variability among countries regarding the price of and access to long-acting insulin analogues, often still much more expensive than human insulin. However, overall use on analogues seems to be expanding and prices decreasing at least for those insulins that are not anymore patent protected". The report also summarizes procurement prices in most WHO regions. Countries that are more likely to reach best insulin prices are those that have adopted insulin price control policies and/or where contract negotiations are supported by competition laws. In these countries, human insulin pen prices can vary between US$ 2 and US$ 5, while analogues pen can vary between US$ 5 and US$ 10. These trends are also reported in other studies. For instance, in Bangladesh, biosimilars of long-acting insulin analogues supported by dedicated policy actions on pharmaceutical cost, cost

about the same as human insulin and represent an increasing market share (*36*). The additional benefit of long-acting insulin analogues in formulations of higher concentrations (300 units/mL versus 100 units/mL) is still unclear and could be a so-called evergreening strategy (extending the life-time of patents about to expire to retain royalties). These higher-concentration products account for increasing large market shares, even though their prices are unlikely to be reduced, as they are under active patent protection (*35*).

The authors of the current application suggest that the EML should be forward-looking and have a reasonable expectation that a product's price will substantially decrease in the near-to-medium-term (e.g. 5 years), particularly if policy approaches favour biosimilars and cost-containment is pursued at the country level. They noted that, "EML listing can serve as a helpful signal to manufacturers of what medicines may benefit the most from generic/biosimilar market entry, as well as a signal to governments as to where interventions in the market are necessary to increase competition or cap prices".

The application also highlights that if long-acting insulins are added to the WHO Model Lists, it is important that individual governments do not interpret this as a recommendation for a wholesale switch from human to analogue insulins, but that long-acting insulins should be included as alternatives. In parallel, countries need to work with manufacturers and other stakeholders to support the availability of human insulin, even in a period in which the use of human insulin is likely to decline.

Availability

Most patents have expired for nearly all insulin analogues (with the exception of formulations with higher concentration of 300 IU/mL), although intellectual property barriers remain in some cases for insulin injection devices (*37*, *38*).

At present, there are no manufacturers of prequalified active pharmaceutical ingredient for insulin or finished pharmaceutical products (*39*, *40*). In 2019, WHO started a pilot project for prequalification of human insulin products, including human insulin, and invited manufacturers to submit an expression of interest (*41*). However, to date, no insulin manufacturers have submitted dossiers for prequalification. There may be many reasons for this apparent lack of interest, for example: (i) being an old, low-cost but also low-profit product, few manufacturers still produce human insulin and the market is dominated by a small number of market leaders who may have little incentive to submit for prequalification; (ii) smaller companies with an established local market may not have ambitions beyond the local market because of costs and regulatory resources; and (iii) manufacturers may not be interested in complying with WHO good manufacturing practice or in investing in improving the product or willing to enter into the commitments that inevitably come with prequalification (variations, reinspections, requalification etc.).

Over the past 2 years, the WHO Prequalification Unit has had the opportunity to exchange information with companies that produce insulin. From this dialogue, interest by manufacturers in a prequalification process that could cover more types of insulin has emerged. Supporting multisourcing tender strategies and accelerating the introduction of multiple types of insulin biosimilars can boost competition. This should include not only the type of insulin itself but also the device used for administration. WHO's prequalification of insulin/devices is a valuable tool to: enhance cooperation between regulators and manufacturers; expand the number of producers of quality-assured insulins and associated devices; and tackle access to insulins in low- and middle-income countries. Including insulin analogues and single-use prefilled syringes/pens as essential medicines can stimulate submissions of dossiers for prequalification from manufacturers.

Other considerations

The Lancet Commission on Diabetes 2020 report (*8*) highlights that basal insulin analogues are better than human or animal insulins for reducing the risk of nocturnal hypoglycaemia. They are especially useful for treatment requiring multiple daily injections of long-/intermediate-acting insulin and short-/rapid-acting insulin at each meal. However, human/biosimilar insulins are more affordable in low- and middle-income countries. The report also notes that in low- and middle-income countries, the dose of premixed insulins may be reduced to avoid hypoglycaemia because of a scarcity of insulin, food insecurity, lack of self-monitoring blood glucose devices and emergency glucagon injection kits, transport difficulties and limited emergency services. "All of these factors can increase the risk of poor glycaemic control and complications that can adversely affect growth and quality of life" (*8*).

The application notes that glucagon is a key treatment for insulin-induced hypoglycaemia; however, availability of glucagon in many low-resource settings is low as it is costly (*4*).

As regards other aspects of treatment, such as diagnostic tests, specialized treatment facilities, administration requirements, monitoring requirements and skill levels of health care providers, these are the same for both human insulins and insulin analogues, except for pen devices that accept replaceable cartridges, which are available only for insulin analogues.

Factors negatively affecting adherence to insulin treatment include complicated dosing regimens, fear of hypoglycaemia events and injection site reactions (*42*). The greater flexibility with long-acting insulin analogues may lead to better adherence and improved quality of life. In addition, in situations where it is less practical or not possible to have 3–4 meals a day (e.g. settings with food insecurity, religious fasting traditions), the flatter time-action curve of long-acting insulin analogues may be particularly valuable.

Committee recommendations

The Expert Committee once again acknowledged that insulin is a life-saving essential medicines for which a strong public health need exists, and equitable and affordable access to insulin globally is still a challenge. The Committee also recalled that the price difference between human insulin and insulin analogues, relative to the magnitude of benefit of insulin analogues, has been the primary reason for the Committee not recommending listing insulin analogues on many occasions in the past.

In its current consideration, the Committee noted that the magnitude of the benefit of insulin degludec, detemir and glargine over human insulin in terms of reduced glycated haemoglobin (a surrogate marker highly correlated with clinical outcomes) remains modest. However, the Committee considered that evidence for an advantage of long-acting insulin analogues over human insulin with regard to a lower incidence of symptomatic and nocturnal hypoglycaemia was consistent and clinically relevant, particularly in the subset of patients with type 1 diabetes who have frequent severe hypoglycaemia (requiring assistance) with human insulin.

In type 2 diabetes, the frequency of severe hypoglycaemia is generally lower than in type 1 diabetes, thus the differences in the rates of hypoglycaemia and severe hypoglycaemia between long-acting analogues and human insulin may be more limited. However, the Committee noted that people with type 2 diabetes with long-lasting insulin deficiency can develop an insulin-dependent disease similar to type 1 diabetes. In these people, the frequency of hypoglycaemia events with human insulin progressively rises, potentially leading to more pronounced benefits of insulin analogues.

The Committee noted that the benefits in terms of reduced hypoglycaemia of different insulin analogues may vary. However, there is currently limited evidence of clear superiority of one analogue over another.

The Committee noted the absence of data from settings with food insecurity where insulin analogues may have greater theoretical advantages, and the lack of experimental studies comparing the long-term outcomes of insulin analogues and human insulin, for example, diabetic complications (nephropathy) or mortality.

With regard to price, the Committee noted that national markets differ considerably in the insulin prices offered to patients and procurers and that insulin analogues are still generally much more expensive than human insulin. However, overall use of insulin analogues is expanding and prices have decreased for insulin analogues that are no longer under patent protection in some markets. In settings where cost-containment actions and efficient procurement negotiations are in place, prices of insulin analogues are aligning with those of human insulin.

The Committee acknowledged that the listing of insulin analogues as alternatives to human insulin may result in a higher proportion of expensive analogue insulins being used, which could have serious implications for affordability for both individuals and health systems. The Committee recommended that the inclusion of insulin analogues in national reimbursement schemes should be planned carefully and be complemented with dedicated cost-containment policies.

The Committee noted and shared the concerns expressed by several stakeholders about potential effects of the inclusion of insulin analogues on the Model Lists on the human insulin market, currently dominated by three pharmaceutical companies, and the financial implications for patients and health systems where insulin analogues are not available or affordable. The Committee was unequivocal that access to affordable human insulin remains a critical priority, globally.

The Committee noted that the efforts made by the WHO Prequalification Unit to prequalify human insulin had not been successful, possibly because of a lack of interest by manufacturers of human insulin, but that interest from manufacturers to prequalify insulin analogues had emerged.

The Committee noted that, while vials have an important role in hospitals, at the community level, prefilled disposable insulin pens and reusable insulin pens with disposable insulin cartridges are preferable. The Committee also noted that access to devices to monitor blood glucose levels is often limited and should be addressed together with interventions to improve access to insulin and injection devices.

Taking all these factors into consideration, the Expert Committee decided to recommend inclusion of long-acting insulin analogues on the core list of the EML and EMLc for the treatment of patients with type 1 or type 2 diabetes mellitus who are at high risk of experiencing hypoglycaemia with human insulin. The Committee considered that this recommendation was adequately supported by the available evidence and is aligned with the recommendation in the WHO guidelines. However, the recommendation did not receive the support of all Committee members, mainly due to concerns about the differences in price and potential effect on the availability of human insulin.

A square box listing was recommended, with therapeutic alternatives limited to insulin degludec, insulin detemir and insulin glargine. The Committee also recommended that quality-assured biosimilars were acceptable alternatives based on evidence of therapeutic equivalence and safety of switching to biosimilars from the reference products. Switching and substitution of reference insulins with biosimilars could result in considerable savings at the country level, with increased access to medicines associated with favourable outcomes.

The Committee noted that the inclusion of long-acting insulin analogues on the Model Lists could facilitate the WHO prequalification process and

recommended that insulin analogues be considered for inclusion in the call for expressions of interest for WHO prequalification.

The Committee recognized the current high price of insulins, both human and analogues, as a barrier to access. The Committee considered that this barrier could be removed or mitigated through multiple actions, including price negotiations, pooled procurement, competitive tendering, support of technology transfer between manufacturers and the increased use of biosimilars. The Committee recommended WHO to continue working on policies and actions that will lead to relevant and rapid price reductions at the country level, based on systematic evaluation of evidence and implementation experiences of countries. The Committee encourages WHO to evaluate the effect of the EML listing of insulin analogues on the global availability, accessibility and price of insulins over a multiyear period. The Committee also highlighted the importance of commitment and action from Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally.

The Committee also considered that insulins could be a priority medicine for the proposed Working Group on high-priced essential medicines. The Working Group, in close coordination with the WHO pricing team, should develop a specific approach to determine fair-price thresholds at the country level for insulins and insulin devices (e.g. pens) and diagnostics (e.g. glucometers), recognizing the valuable role WHO can play in monitoring and defining fair prices, facilitating access and supporting progress towards universal health coverage.

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18.5.2 Antiretrovirals

Sodium-glucose cotransporter-2 (SGLT2) inhibitors – addition – EML

Empagliflozin **ATC Code: A10BK03**

Proposal

Addition of empagliflozin as the representative of the pharmacological class of sodium-glucose co-transporter-2 (SGLT2) inhibitors on the core list of the EML as add-on treatment for adults with type 2 diabetes who have or are at a high risk of cardiovascular disease and/or diabetic nephropathy. Therapeutic alternatives are limited to canagliflozin and dapagliflozin.

Applicant

The International Diabetes Federation (IDF)

WHO technical department

Management of Noncommunicable Diseases

EML/EMLc

EML

Section

18.5.2 Oral hypoglycaemic agents

Dose form(s) & strength(s)

Empagliflozin: tablet 10 mg, 25 mg
Canagliflozin: tablet 100 mg, 300 mg
Dapagliflozin: tablet 5 mg, 10 mg

Core/complementary

Core

Individual/square box listing

Square box listing for empagliflozin as the representative medicine, with canagliflozin and dapagliflozin as therapeutic alternatives.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

In 2013, the Expert Committee evaluated evidence comparing alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4), meglitinides and thiazolidinediones with metformin and sulfonylureas (*1*). The Committee

concluded that "there was insufficient evidence to show that any of the medicines in the four groups (alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, meglitinides, or thiazolidinediones) offered any efficacy or safety advantages over the existing medicines included in the EML" (i.e. metformin first-line therapy and sulfonylurea second line). SGLT2 inhibitors were not included in the review as they had not entered the market at that time.

In 2017, the Committee considered a review of medicines for second-line therapy for type 2 diabetes, including alpha-glucosidase inhibitors, basal, bolus and biphasic human insulins, analogue insulins, DPP-4 inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), meglitinides, SGLT2 inhibitors and thiazolidinediones based on an update of the 2013 review by the Canadian Agency for Drugs and Technologies in Health (*2*, *3*). The Expert Committee did not recommend the inclusion of second-line medicines for type 2 diabetes on the EML, and confirmed the role of sulfonylureas as one of the most cost-effective treatments for intensification therapy of type 2 diabetes. However, the Committee noted that SGLT2 inhibitors had shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality. The Committee considered that this finding needed to be confirmed with data from other trials before this class of medicines could be supported for inclusion on the EML (*4*).

These data are now available with several reviews demonstrating cardiovascular and renal benefits of SGLT2 inhibitors. Consequently, these agents are routinely recommended by international guidelines. Empagliflozin was the first of these agents to demonstrate cardiovascular benefits (*5*).

Public health relevance (burden of disease)

Worldwide, diabetes affected an estimated 463 million people in 2019 (9.3% of the global population), of whom 79% live in low- and middle-income countries (*6*). The number of people with diabetes has almost tripled in the past 3 decades due to: increase in population size; population ageing; and the increasing prevalence of the main risk factors for diabetes – overweight, obesity and physical inactivity (*7*). In 2019, diabetes was responsible for over 1.5 million deaths and 2.79% of all global disability-adjusted life years (*8*). The burden of diabetes is projected to increase to affect 700 million people in 2045 (*9*).

Diabetes is estimated to reduce life expectancy by 6 years when diagnosed at 40 years (*10*), and is a major cause of peripheral neuropathy, blindness, kidney failure and lower limb amputation. Diabetes complications affect quality of life and often lead to premature deaths, which is experienced by about a half of all people with diabetes.

The incidence and prevalence of type 2 diabetes are much higher than type 1 diabetes, with type 2 diabetes responsible for about 90–95% of all

diabetes cases (*6*).The annual global expenditure on health care for people with diabetes is estimated to be US$ 850 billion, 12% of the overall global health care expenditure (*9*).

Summary of evidence: benefits (from the application)

Systematic reviews and meta-analyses

A systematic review and network meta-analysis of 730 trials (402 030 participants) compared 11 glucose-lowering medicines added to background therapy as part of a guideline development process for the Australian evidence-based clinical guidelines for diabetes (*11*).

For the clinical question, "Should GLP-1 receptor agonist, SGLT2 inhibitors, sulfonylurea or DPP-4 inhibitor be used as an add-on in adults with type 2 diabetes? Will it differ by cardiovascular risk groups?", the following findings were reported.

- SGLT2 inhibitors lowered the odds of all-cause mortality compared with placebo, DPP-4 inhibitors, GLP-1 RAs or sulfonylureas as add-on therapy (high-certainty or moderate-certainty in lowest-risk patients because of indirectness).
- SGLT2 inhibitors lowered the odds of hospitalization for heart failure compared with placebo, DPP-4 inhibitors, GLP-1 RAs or sulfonylureas when added to background treatment (high-certainty or moderate-certainty in lowest-risk patients because of indirectness).
- There was no evidence that SGLT2 inhibitors lowered the odds of a major adverse cardiovascular event (three-item major adverse cardiovascular events – composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) compared with placebo when added to background therapy (moderate-certainty evidence because of imprecision).
- SGLT2 inhibitors probably lowered the odds of a major adverse cardiovascular event (four-item major adverse cardiovascular events: three-item plus hospitalization for unstable angina) compared with placebo or a GLP-1 RAs added to background therapy (high-certainty and moderate-certainty evidence in lowest-risk patients because of indirectness).
- There was no evidence that an SGLT2 inhibitor added to background therapy increased severe hypoglycaemia more than placebo (high-certainty or moderate-certainty evidence in lowest-risk patients because of indirectness).

- SGLT2 inhibitors decreased kidney failure compared with placebo when added to background therapy (high-certainty or moderate-certainty evidence in lowest-risk patients because of indirectness).
- SGLT2 inhibitor therapy decreased HbA1c compared with standard therapy (high-certainty evidence).
- The odds of serious adverse events were lower with SGLT2 inhibitors than standard care (high-certainty or moderate-certainty in lowest-risk patients because of indirectness). There was no evidence that other therapies added to background therapy had different odds of serious adverse events (high-certainty evidence).

Based on these findings, the guideline group made a strong recommended for the addition of an SGLT2 inhibitor to other glucose-lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.

A 2021 systematic review and network meta-analysis of 764 trials (421 346 participants) compared SGLT2 inhibitors or GLP-1 RAs with placebo, standard care or other glucose-lowering treatments in adults with type 2 diabetes with varying cardiovascular and renal risks (*12*). The results are summarized In Table 8 for the addition of SGLT2 inhibitors to existing diabetes treatment.

Table 8

Cardiovascular and renal outcomes in adults with type 2 diabetes treated with SGLT2 inhibitors compared with placebo or GLP-1 RAs

Measure	OR (95% CI)	Fewer events/1000 in 5 years, no. (type of patient)
All-cause mortality	238 trials including 290 662 patients	
SGLT2 vs placebo	0.77 (0.71 to 0.83)	5 (very low risk – moderate-certainty evidence); 15 (low risk); 25 (moderate risk); 34 (high risk); 48 (very high risk – high-certainty evidence)
SGLT2 vs GLP-1 RAs	0.88 (0.79 to 0.97)	2 (very low risk patients); 7 (low risk); 12 (moderate risk); 16 (high risk) and 23 (very high risk) – all moderate- to high-certainty evidence

Table *continued*

Measure	OR (95% CI)	Fewer events/1000 in 5 years, no. (type of patient)
Cardiovascular mortality	135 trials including 226 701 patients	
SGLT2 vs placebo	0.84 (0.76 to 0.92)	2 (very low risk patients); 7 (low risk); 12 (moderate risk); 16 (high risk) and 24 (very high risk) – all moderate- to high-certainty evidence
SGLT2 vs GLP-1 RAs	0.96 (0.84 to 1.09)	ND – moderate- to high-certainty evidence
Non-fatal myocardial infarction	208 trials including 265 921 patients	
SGLT2 inhibitors vs placebo	0.87 (0.79 to 0.97)	4 (very low risk patients); 7 (low risk); 13 (moderate risk); 14 (high risk) and 21 (very high risk) – all moderate- to high-certainty evidence
SGLT2 vs GLP-1 RAs	0.95 (0.84 to 1.08)	ND – moderate- to high-certainty evidence
Non-fatal stroke	176 trials including 261 434 patients	
SGLT2 inhibitors vs placebo	1.01 (0.89 to 1.14)	ND – moderate- to high-certainty evidence
SGLT2 vs GLP-1 RAs	1.20 (1.03 to 1.41)	NA, more events with SGLT2 – moderate- to high-certainty evidence
Kidney failure	33 trials including 98 284 patients	
SGLT2 inhibitors vs placebo	0.71 (0.57 to 0.89)	1 (very low risk patients); 3 (low risk); 6 (moderate risk); 25 (high risk) and 38 (very high risk) – all moderate- to high-certainty evidence
SGLT2 vs GLP-1 RAs	0.91 (0.69 to 1.20)	ND – low- to moderate-certainty evidence

Table *continued*

Measure	OR (95% CI)	Fewer events/1000 in 5 years, no. (type of patient)
Hospital admission for heart failure	149 trials including 242 361 patients	
SGLT2 inhibitors vs placebo	0.70 (0.63 to 0.77)	2 (very low risk patients); 9 (low risk); 23 (moderate risk); 29 (high risk) and 58 (very high risk) – all moderate- to-high-certainty evidence
SGLT2 vs GLP-1 RAs	0.74 (0.65 to 0.85)	1 (very low risk patients); 7 (low risk); 18 (moderate risk); 24 (high risk) and 48 (very high risk) – all moderate to high-certainty evidence
	Mean difference (95% CI)	**Certainty of evidence**
Body weight	469 trials including 226 361 patients[a]	
SGLT2 inhibitors vs placebo	−1.92 kg (−2.23 to −1.62)	Low
SGLT2 vs GLP-1 RAs	0.47 kg (−0.85 to −0.09)	Moderate
Glycated haemoglobin A1c	604 trials including 242 745 patients[a]	
SGLT2 inhibitors vs placebo	−0.60% (−0.67 to −0.54)	Low
GLP-1 RAs vs SGLT2	−0.28% (−0.37 to −0.19)	High

OR: odds ratio; CI: confidence interval; SGLT2: sodium-glucose co-transporter-2; GLP-1 RAs: glucagon-like peptide 1 receptor agonists; ND: no difference; NA: not applicable.

[a] For a median follow-up of 6 months.

Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. (*12*).

The 2020 Kidney Disease Improving Global Outcomes (KDIGO) guidelines include a level 1 (strong) recommendation for treating patients with type 2 diabetes who have an estimated glomerular filtration rate greater than 30 mL/min per 1.73m² with an SGLT2 inhibitor (*13*). This recommendation was based on the demonstrated cardiovascular benefits reported for SGLT2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) from numerous randomized controlled trials (*5*, *14*–*18*). The benefits of SGLT2 were also reported in a real-world registry study, with reduced risks of hospitalization for

heart failure and cardiovascular mortality (*19*). Benefits for the kidneys were also demonstrated in studies with prespecified renal outcomes: (i) empagliflozin was associated with a lower risk of incident or worsening nephropathy compared with placebo (–12.7% versus 18.8%, hazard ratio (HR) 0.61, 95% CI 0.53 to 0.70) (*20*); (ii) canagliflozin was associated with a lower risk of progression of albuminuria (HR 0.73, 95% CI 0.67 to 0.79), and a lower risk of the composite outcome of 40% reduction in estimated glomerular filtration rate, need for kidney replacement therapy or death from renal cause (HR 0.60, 95% CI 0.47 to 0.77) (*16*); and (iii) dapagliflozin was associated with a lower risk of the composite outcome of 40% reduction in estimated glomerular filtration rate to < 60 mL/min per 1.73m², end-stage kidney disease and cardiovascular or renal death (HR 0.67, 95% CI 0.67 to 0.87) (*15*).

A systematic review and meta-analysis of four randomized controlled trials of SGLT2 inhibitors examined kidney outcomes in individuals with and without chronic kidney disease (*21*). For the subgroup of patients with an estimated glomerular filtration rate of 30 to < 60 mL/min per 1.73m², SGLT2 inhibitors were associated with a reduced risk of adverse kidney outcomes – worsening kidney failure, end-stage kidney disease or renal death – HR 0.76, 95% CI 0.51 to 0.89). Other trials of SGLT2 inhibitors in patients with chronic kidney disease also demonstrated better renal outcomes in the SGLT2 arms (*16*, *22*). In addition, real-world data suggest that the renal benefits of SGLT2 inhibitors are generalizable to clinical practice (*23*).

Summary of evidence: harms (from the application)

The most common adverse events with SGLT2 inhibitors are genital infections related to glycosuria. The increased risk of genital mycotic infections with SGLT2 inhibitors in both men and women is consistent across all clinical trials. SGLT2 inhibitors increased genital infection compared with placebo with high-certainty, resulting in 143 more genital infections per 1000 patients treated for 5 years (*12*).

Fournier gangrene, an aggressive and life-threatening necrotizing fasciitis of the external genitalia, perineum and perianal region, is a serious but rare adverse event associated with the use of SGLT2 inhibitors. This condition is much more common in men than in women, and diabetes is a predisposing factor. In 2018, the United States Food and Drug Administration required a warning about the risk of Fournier gangrene to be added to the prescribing information of all SGLT2 inhibitors. In a postmarketing review, 55 cases of Fournier gangrene were identified by the Food and Drug Administration in 6 years of SGLT2 inhibitor use compared with 19 cases over 35 years for all other drugs that lower blood glucose (*24*).

High-quality evidence from a systematic review and meta-analysis of 39 randomized controlled trials (60 580 patients) reported an increased risk of

diabetic ketoacidosis with SGLT2 inhibitors compared with placebo or other antidiabetic drugs (Peto OR 2.13, 95% CI 1.38 to 3.27), with an absolute rate of three events per 1000 patients over 5 years (*25*). In May 2015, the Food and Drug Administration issued a drug safety communication warning that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis (*26*).

An increased risk of bone fractures and lower-limb amputations associated with canagliflozin was reported in one randomized controlled trial (*14*). Subsequent meta-analyses and real-world data, however, did not identify an increased risk of bone fractures in patients treated with SGLT2 inhibitors (*27*,*28*). A systematic review of seven randomized controlled trials suggested no statistically significant association between exposure to SGLT2 inhibitors and lower-limb amputations. However, subgroup analysis of canagliflozin versus placebo indicated a statistically significant increased risk (*29*). The Food and Drug Administration warning on canagliflozin about the increased risk of amputations was removed in 2020 (*30*).

The Australian guideline review found moderate- to high-certainty evidence that SGLT2 inhibitors have lower odds of serious adverse events than standard care, and high-certainty evidence that there was no evidence that other therapies added to background therapy had different odds of serious adverse events. In addition, there was no evidence that an SGLT2 inhibitor added to background therapy increased severe hypoglycaemia more than placebo (*11*).

A 2020 study analysed the safety and tolerability of empagliflozin compared with placebo by pooling data from clinical trials. The frequency of serious adverse events requiring hospitalization was 18.6% for the empagliflozin group and 21.3% for the placebo group. Empagliflozin was not associated with a higher rate of confirmed hypoglycaemia compared with placebo, except in patients also receiving insulin and/or a sulfonylurea. The incidence or urinary tract infections was similar between groups. Genital infections occurred more frequently in patients treated with empagliflozin. Volume depletion events were similar across groups but were more frequent with empagliflozin in patients aged 75–85 years and those on loop diuretics at baseline (*31*).

Additional evidence (not in the application)

Not applicable.

WHO guidelines

In 2018, WHO published guidelines on pharmacological agents for managing hyperglycaemia in type 1 and type 2 diabetes for use in primary health care in low-resource settings (*32*). Several newer oral agents were reviewed, including DPP-4 inhibitors, SGLT2 inhibitors and thiazolidinediones. GLP 1 RAs were outside the scope of these guidelines.

The guideline group acknowledged that SGLT2 inhibitors look particularly promising. Empagliflozin, when compared with placebo, had a protective effect on a composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in one study in people with type 2 diabetes at high cardiovascular risk (*5*). However, more evidence was needed to determine whether this was a class effect and whether there was a cardioprotective effect in the general population of people with type 2 diabetes.

The WHO guideline group considered insulin to be comparable to SGLT2 inhibitors when weighing desirable and undesirable effects. Insulin and thiazolidinediones were most effective at lowering HbA1c, while DPP-4 inhibitors and SGLT2 inhibitors were better than thiazolidinediones in lowering body weight (*33*).

Based on these data, the following recommendations were made for the second- and third-line treatment of type 2 diabetes (*32*).

- Give a sulfonylurea to patients with type 2 diabetes who do not achieve glycaemic control with metformin alone or have contraindications to metformin (strong recommendation, moderate-quality evidence).
- Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence).
- If insulin is unsuitable, a DPP-4 inhibitor, SGLT2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence).

Costs/cost–effectiveness

The cost–effectiveness of SGLT2 inhibitors has been studied in recent systematic reviews and a meta-analyses (*34–36*). Most studies identified found SGLT2 inhibitors to be cost-effective compared with older classes of second-line glucose-lowering medicines, especially for patients at a high risk of developing cardiovascular disease. Beyond glucose-lowering effects, the beneficial effects of SGLT2 inhibitors on renal function, cardiovascular outcomes and obesity are key drivers of cost–effectiveness.

Estimates of the cost–effectiveness of SGLT2 inhibitors outside high-income countries are limited. Low- and middle-income countries are likely to have lower willingness-to-pay thresholds for cost–effectiveness, and SGLT2 inhibitors will have to have significantly lower prices in low- and middle-income countries than the current originator prices in high-income countries in order to be cost-effective.

In 2018, the Medicines Patent Pool published a feasibility study examining the SGLT2 inhibitor market in detail, in terms of patient access to SGLT2 inhibitors (at the time), pricing, the intellectual property landscape, and potential clinical benefits and cost savings if access were expanded by voluntary licensing through the Medicines Patent Pool model. The Medicines Patent Pool estimated that SGLT2 inhibitor prices could decrease substantially when and where competitive generic manufacture is established (*37*).

Availability

SGLT2 inhibitors have wide global regulatory approval.

Empagliflozin (Jardiance®, Boehringer Ingelheim) has primary patent protection until 2025.

Canagliflozin (Invokana®, Janssen) has primary patent protection until 2024.

Dapagliflozin (Farxiga®, Bristol-Myers Squibb) has primary patent protection until 2020–2023.

Other considerations

Not applicable

Committee recommendations

Since SGLT2 inhibitors were last reviewed by the Expert Committee in 2017, new evidence has confirmed the positive effect of SGLT2 inhibitors compared with placebo on all-cause mortality, cardiovascular outcomes (cardiovascular mortality, non-fatal myocardial infarction and hospital admission for unstable angina), renal outcomes (kidney failure, end-stage renal disease and renal death), body weight and HbA1c.

Based on this new evidence, the Expert Committee had increased confidence in the cumulative estimates and overall evidence for relevant clinical benefits associated with SGLT2 inhibitors as add-on therapy. The Committee noted that the situation is less clear when comparing SGLT2 inhibitors with GLP-1 RAs, although the SGLT2 inhibitors seem to be the preferred option as they are consistently associated with favourable results for most cardiovascular outcomes and are orally administered in contrast to GLP-1 RAs that need to be injected.

The Committee considered that SGLT2 inhibitors are associated with some relevant adverse events such as urogenital infections, Fournier gangrene, osmotic diuresis and euglycaemic diabetic ketoacidosis. However, overall, the benefit-to-risk ratio favours SGLT2 inhibitors, particularly in patients with cardiovascular and kidney disease. While prices are substantially higher than for the oral hypoglycaemic agents currently listed on the EML (metformin and sulfonylureas), cost–effectiveness analyses, mainly conducted in high-income

countries, suggest favourable incremental cost–effectiveness ratios at usual willingness-to-pay thresholds, given the effect of SGLT2 inhibitors on hard clinical outcomes.

The Expert Committee therefore recommended the inclusion of SGLT2 inhibitors on the core list of the EML as a second-line therapy for patients with type 2 diabetes who have not achieved appropriate glycaemic control with metformin or a sulfonylurea. High-quality evidence shows there are clinically beneficial effects in this population, particularly in those at high risk of cardiovascular events and/or diabetic nephropathy, and there is a reasonable safety profile. The Committee recommended listing empagliflozin as the representative of the pharmacological class, with canagliflozin and dapagliflozin as therapeutic alternatives.

The Expert Committee also recommended that the Medicines Patent Pool explores how to facilitate affordable access to SGLT2 inhibitors in low- and middle-income countries through public health-oriented licences with the companies holding the patents.

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Section 19: IMMUNOLOGICALS

19.2 Sera, immunoglobulins and monoclonal antibodies

Anti-rabies virus monoclonal antibodies – addition – EML and EMLc

Anti-rabies virus monoclonal antibodies **ATC Code: to be assigned**

Proposal

Addition of anti-rabies virus monoclonal antibodies (ARV mAbs) to the core list of the EML and EMLc for postexposure prophylaxis of rabies virus infection.

Applicant

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Erin Sparrow; WHO Department of Immunization, Vaccines and Biologicals

WHO technical department

Control of Neglected Tropical Disease
Immunization, Vaccines and Biologicals

EML/EMLc

EML and EMLc

Section

19.2 Sera, immunoglobulins and monoclonal antibodies

Dose form(s) & strength(s)

Injection: 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human)

Injection: 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine)

Core/complementary

Core

Individual/square box listing

Individual, including quality-assured biosimilars

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

ARV mAbs have not previously been considered by the Expert Committee for inclusion on the Model Lists.

Public health relevance (burden of disease)

Rabies is a preventable viral zoonotic disease and is a neglected tropical disease. It is responsible for an estimated 59 000 human deaths annually, mostly in countries in Africa and Asia (*1*). Most human rabies cases result from dog bites. After the onset of clinical symptoms, the disease is almost always fatal. Survival from clinical rabies has been documented in only 15 cases, with severe sequelae in most (*2*).

While rabies control depends heavily on prevention of canine rabies by mass vaccination, postexposure prophylaxis of humans who have been bitten by an animal is a highly effective preventive intervention. After a bite exposure, postexposure prophylaxis involves the combined use of extensive wound washing, infiltration of rabies immunoglobulin (RIG) and administration of modern tissue culture vaccines (*3*).

Globally, an estimated 29.2 million people receive postexposure prophylaxis for rabies annually (*1*). Current WHO postexposure prophylaxis recommendations include thorough wound washing, rabies vaccination and infiltration of RIG (*3*).

Historically, failure of postexposure prophylaxis in humans is rare when these treatments are performed promptly and properly, even after severe exposures (*4–6*). Since the introduction of modern cell culture vaccines and RIG in the late 1970s, no failures have been reported within enzootic developed countries, such as those in Europe and North America. When postexposure prophylaxis failures are reported in less developed countries, most reports are related to the lack of the use of RIG in bite victims.

Historically, WHO recognized three classes of biological products as available for the passive immunization component of postexposure prophylaxis: human RIG (hRIG), intact equine RIG (eRIG) and highly purified fragments (F(ab′)2) produced from eRIG. Production capacity and cost limit the availability of these serum-derived polyclonal RIGs, with most less developed countries that have a high incidence of rabies reporting negligible use. Understandably, in less developed countries, cost is an important reason why RIG is not used during postexposure prophylaxis (*7*). For example, a study in India found that only 21 of 783 (2.7%) patients with bites where there was a risk of rabies virus being present were prescribed hRIG, and only 10 could afford to obtain the product (*8*). Survival outcome of these patients was not provided in this study. Other studies in India and Thailand have also shown that only 2–3% of patients with severe animal bites receive RIG (*9*, *10*).

The inclusion of ARV mAbs in human postexposure prophylaxis is an opportunity for large-scale production of safe, effective, well characterized, dependable and uniform biological medicines, which would likely lead to lower long-term manufacturing costs (*11*).

Summary of evidence: benefits (from the application)

ARV mAbs were first produced during the late 1970s (*12*). Some ARV mAbs only recognized very distinctive epitopes on a given rabies virus variant. Other cross-reactive ARV mAbs, directed to the outer viral glycoprotein, more broadly neutralized global rabies viruses of public health relevance, and were shown to protect laboratory animals even after severe experimental viral exposure (*13*). After years of development, the first ARV mAbs to be used in humans was a mix of two such antibodies, CR57 and CR 4098 (together called CL184), which were shown to have broad neutralizing activity for many rabies virus isolates during preclinical research (*14*, *15*). Dose-ranging studies conducted in animals showed that a dose of 12 micrograms/kg in combination with vaccination was non-inferior to RIG and vaccination. Both phase I and II trials, conducted in India, Philippines and the United States of America, showed these ARV mAbs were safe and well tolerated, and had adequate levels of rabies virus neutralizing activity in all participants, with doses of CL184 of 20 IU/kg or 40 IU/kg. The product was withdrawn from further clinical development after changes in pharmaceutical company ownership. Thereafter, given the potential shown by CL184, other ARV mAbs, directed against the outer rabies virus glycoprotein, have proven to be an effective and safe option for use in postexposure prophylaxis, as an alternative to equine and human RIG (*16*).

Several studies (published and unpublished) have shown ARV mAbs to have a similar effectiveness as RIG.

A phase I simulated postexposure prophylaxis study in India of 74 adults found a single ARV mAb induced rabies virus neutralizing activity comparable with a regimen containing RIG (*17*). A phase II/III, single-blind, randomized, non-inferiority study was conducted in India with 200 participants (adults and children > 5 years) with suspected WHO category III rabies virus exposures (*18*). Participants received either ARV mAbs or RIG (1:1 ratio) in wounds and, if required, intramuscularly on day 0, together with five doses of rabies vaccine on days 0, 3, 7, 14 and 28. The primary endpoint was the ratio of the day 14 geometric mean concentration of rabies virus neutralizing activity, as measured in ARV mAb recipients relative to RIG recipients. Of 199 participants, 101 received ARV mAbs and 98 received RIG together with at least one dose of vaccine. The day 14 geometric mean concentration ratio of rabies virus neutralizing activity for the ARV mAb group relative to the RIG group was 4.23 (97% confidence interval (CI) 2.59 to 6.94): geometric mean concentration of 24.9 IU/mL (95% CI 18.94 to 32.74) for ARV mAb recipients and 5.88 IU/mL (95% CI 4.11 to 8.41) for RIG recipients. No deaths from rabies were reported.

Another phase III, multicentre, randomized controlled, non-inferiority study compared ARV mAbs plus vaccine to RIG plus vaccine in 308 participants

with category III rabies virus exposure (*19*). Participants were randomized to receive either ARV mAbs (docaravimab and miromavimab) or hRIG, in a 1:1 ratio. The primary endpoint was comparison of responder rates between the two arms of the study, assessed as the percentage with rabies virus neutralizing antibodies titres ≥ 0.5 IU/mL on day 14. ARV mAbs were found to be non-inferior to hRIG, with 90.3% and 94.4% of participants, respectively, with antibody titres ≥ 0.5 IU/mL on day 14 (95% CI −0.02 to 0.10). No deaths or rabies cases were reported.

A potential disadvantage is that polyclonal antibodies are thought to neutralize more lyssavirus variants than monoclonal antibodies (*16*). Researchers have attempted to address the reactivity of these biological medicines by using in vitro neutralization tests and various experimental animal models with a broad number of viral isolates to help provide reassurance of the extent of protection monoclonal antibodies provide compared with polyclonal antibodies. All ARV mAbs considered for human use have been shown to neutralize rabies virus in the geographical regions where trials were conducted, most significantly for canine rabies virus variants which cause most of the human deaths from rabies globally (*14*, *20–23*). Enhanced surveillance and pathogen discovery activities (using genomic sequencing) continue to characterize local viruses and coverage by available products to ascertain the public health relevance of lyssavirus antigenic diversity and neutralization coverage by existing monoclonal antibodies.

Summary of evidence: harms (from the application)

To date, no serious adverse events have been reported from the use of ARV mAbs in humans. Most reactions reported were mild to moderate in severity and resolved without sequelae in a short time (*17–19*, *24*).

In a comparative clinical trial in India, 461 adverse events were reported, of which 83.7% were solicited events and 16.3% were unsolicited events (*18*). Of the 386 solicited events reported within the first 7 days of postexposure prophylaxis, 250 (64.8%) were injection site reactions (112 at the wound site, 40 at another site where any remaining RIG or ARV mAb was injected and 98 at the site of rabies vaccine injection). The other 136 (35.2%) solicited events were systemic reactions – 85 from 28 participants in the ARV mAb group and 51 from 20 participants in the RIG group. All solicited reactions were of mild to moderate severity, except for three events of redness, one event of pain and one case of fever (41.3 °C) which were assessed as severe – all were in the RIG group. Of the 75 unsolicited events reported from 57 participants during the 84-day study period, all were assessed as unrelated to the study treatment except for two: itching at a wound site in one participant in the ARV mAb group and pain at the injection site in one participant in the RIG group. The mean changes in haematology and chemistry parameters from day 0 to day 28 were comparable between the two groups. No antidrug antibodies were detected in any of the study participants.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO recommendations on anti-rabies postexposure prophylaxis are given in its rabies vaccine position paper and were last updated in 2018 (*3*). Use of ARV mAb products instead of RIG is encouraged, if available.

Costs/cost–effectiveness

Few data are available on the comparative costs and effectiveness of ARV mAbs. To date, only two ARV mAb products have been licensed and marketed in India, so prices from a wider range of settings are not available. Moreover, similar to RIG, the use of ARV mAbs usually occurs only once in a person's life-time, after exposure but before illness onset. Therefore, any cost–effectiveness estimate is based only on the cost per case in light of the clinical event prevented, which is considered lifesaving with timely and appropriate postexposure prophylaxis.

Postexposure prophylaxis is considered to be a cost-effective strategy to prevent deaths in people with WHO category III exposure to rabies virus (*25*). The ability to pay for postexposure prophylaxis varies widely across the world. Studies on willingness-to-pay postexposure prophylaxis thresholds have been reported as US$ 1400 in United Republic of Tanzania (*26*) and US$ 2953 in the Philippines (*27*).

In most less developed countries in Africa and Asia, availability of RIG is very limited and it varies greatly in price from US$ 15 to US$ 70 per vial (*28*).

It is anticipated that the price of ARV mAbs will be in between the prices of hRIG and eRIG. For example, in India, an estimate for a routine course postexposure prophylaxis for an average-sized adult is US$ 285 for hRIG, US$ 55 for ARV mAbs and US$ 13 for eRIG.

Availability

Two ARV mAb products are currently registered for use in humans.

- 17C7 (also known as RAB1, SIIRMAB or Rabisheld), a homologous human ARV mAb for adult and paediatric use. It is licensed in India and is also registered for use in Bahrain, Chad, Democratic Republic of the Congo, Ethiopia, Georgia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Nepal, Oman, Tajikistan, Tanzania and Uzbekistan.
- M777-16-3/62-71-3 (docaravimab and miromavimab, also known as Rabimab, Twinrab), a heterologous mix of two murine ARV mAbs for adult and paediatric use. It is licensed in India.

Two other ARV mAbs are currently under clinical and/or regulatory evaluation.

Other considerations

Not applicable

Committee recommendations

The Expert Committee acknowledged the public health need for effective interventions for rabies postexposure prophylaxis, noting that the case fatality of rabies infection is almost 100% after the onset of clinical symptoms.

The Committee considered that the availability of a range of alternative options for use in rabies postexposure prophylaxis (human RIG, equine RIG and ARV mAbs) on the EML and EMLc would facilitate access to treatment. The inclusion of ARV mAbs will potentially address some of the supply and production limitations currently experienced with hRIG and eRIG by increasing procurement options. It was also noted that ARV mAbs could be procured at lower cost than human RIG (but higher cost than equine RIG).

The Committee noted that the clinical evidence supporting the use of ARV mAbs is from trials assessing rabies virus neutralizing activity, using an in vitro correlate of protection that has been accepted by WHO and regulatory agencies as a study endpoint in clinical trials of novel rabies vaccines or RIG products. The Committee also noted that there was no indication of an increase in mortality from postmarketing surveillance.

The Committee acknowledged that evidence on efficacy and safety for use in children, the elderly or pregnant women was lacking, but was reassured by the technical unit that children were included in the trial populations, however the data had not yet been stratified. Moreover, the Strategic Advisory Group of Experts (SAGE) on Immunization recommended postmarketing surveillance of these products due to their potential adverse effects.

The Committee noted that the 2018 WHO position paper on rabies encourages the use of ARV mAbs as an alternative to RIG and that having access to RIG and ARV mAbs may ensure adequate supply at the global level. The Committee also noted that WHO prequalification processes for monoclonal antibodies for infectious diseases are planned in 2022, to facilitate access to affordable and quality-assured products.

Therefore, the Expert Committee recommended the inclusion of ARV mAbs (murine and human formulations), including quality-assured biosimilars, on the core list of the EML and EMLc for use as part of rabies postexposure prophylaxis, in line with WHO recommendations.

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Equine rabies immunoglobulin – addition – EML and EMLc

Equine rabies immunoglobulin **ATC Code: J06BB05**

Proposal

Reinstatement of equine rabies immunoglobulin (eRIG) to the EML and EMLc for postexposure prophylaxis of rabies virus infection.

Applicant

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Control of Neglected Tropical Disease
Immunization, Vaccines and Biologicals

EML/EMLc

EML and EMLc

Section

19.2 Sera and immunoglobulins

Dose form(s) & strength(s)

Injection: 150 IU/mL, 200 IU/mL, 300 IU/mL, 400 IU/mL in vial

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

The 2019 Model Lists include only human rabies immunoglobulin (Section 11.2.1 Human immunoglobulins). Rabies immunoglobulin (without specification of human or equine) has been included on the Model Lists since 1992. In 2013, the listing was changed to specify human rabies immunoglobulin, thereby excluding eRIG.

Public health relevance (burden of disease)

Rabies is a preventable viral zoonotic disease and a neglected tropical disease. It is responsible for an estimated 59 000 human deaths annually, mostly in countries in Africa and Asia (*1*). Most human rabies cases result from dog bites. After the onset of clinical symptoms, the disease is almost always fatal. Survival from clinical rabies has been documented in only 15 cases, mostly with severe sequelae (*2*).

While rabies control depends heavily on prevention of canine rabies by mass vaccination, postexposure prophylaxis of humans who have been bitten by an animal is a highly effective preventive intervention. After a bite exposure, postexposure prophylaxis involves the combined use of extensive wound washing, infiltration of rabies immunoglobulin and administration of modern tissue culture vaccines (*3*).

The role of RIG in passive immunization is to provide neutralizing antibodies at the site of exposure before patients start producing vaccine-induced antibodies.

Summary of evidence: benefits (from the application)

Purified eRIG is highly effective, as evident after decades of clinical use (*4*). A 2013 study compared the neutralization effectiveness of reduced eRIG and hRIG in cell culture and in mice: in vitro, neutralization of rabies virus by eRIG and hRIG were identical, while in vivo, full protection was conferred by both eRIG and hRIG (*5*). Moreover, no vaccine was administered to those animals that received RIG, yet the experimental groups that received at least 0.025 IU/100 microlitres of either eRIG or hRIG showed 100% survival, compared with 100% mortality in the control group.

Today, modern eRIG is highly purified and enzyme-refined and contains over 85% antigen-binding immunoglobulin fragments – F(ab′)2 (*6–8*).

Although these F(ab′)2 fragments may have a shorter half-life in vivo than intact immunoglobulin, these fragments have a higher specificity and instances of antigen-binding reactions, and therefore efficacy is preserved (*8*). The relative efficacy of eRIG is strongly supported, especially considering the price and scarcity of hRIG and the nearly 100% case-fatality of clinical rabies.

Summary of evidence: harms (from the application)

Long-standing biomedical data support the relative safety of eRIG in human rabies postexposure prophylaxis (*9*).

In the past, crude horse serum and unpurified eRIG were associated with serum sickness, anaphylaxis and other severe adverse reactions (*5*). Through techniques such as heat treatment, pepsin digestion and enzyme refinement, the immunoglobulin crystallizable fragment (Fc) is removed and the nonspecific

protein content of the purified serum is reduced to less than 3% (*10*). As the Fc fragment in unpurified eRIG is responsible for direct complement activation and anaphylactic reactions, the high F(ab′)2 content and low Fc proteins allow for increased safety and specific activity (*5*, *8*).

This eRIG treatment has been shown to be safe for pregnant women, as the F(ab′)2 immunoglobulin fragments do not cross the placenta (*11*).

Studies to date suggest that severe adverse reactions with eRIG, such as serum sickness and anaphylaxis, are infrequent (*12*). Other adverse events tend to be mild, not life-threatening and easily resolved, such as local pain, redness, induration, fever and pruritus (*8*, *10*–*16*). Clinical studies show that the incidence of anaphylaxis with eRIG is similar to that associated with the use of penicillin (*17*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO recommendations on the use of RIG in postexposure prophylaxis are given in the rabies vaccine position paper and were last updated in 2018 (*3*). Changes were based on functional use, mainly in that the dose of RIG is now determined taking account of the anatomical feasibility of administration in and around the affected area instead of on the patient's total body weight.

WHO recommends the use of RIG as part of postexposure prophylaxis in immunologically naïve individuals with category III rabies virus exposure, defined as single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure). RIG is not indicated for previously immunized individuals.

RIG should be administered only once, preferably at, or as soon as possible after, the start of postexposure prophylaxis. RIG should not be given after day 7 following the first rabies vaccine dose, because circulating antibodies will have begun to appear.

In almost all cases, the amount of RIG administered is based on the location and extent of the lesions, where the rabies virus is localized after exposure. For small wounds, the maximum quantity of RIG that is anatomically feasible should be administered. Only the maximum dose of RIG is still assessed by body weight (e.g. 20 IU/kg for hRIG and 40 IU/kg for eRIG).

Skin testing before eRIG administration should not be done because it is unreliable in predicting adverse effects. However, the treating physicians should be prepared to manage anaphylaxis, which, although rare, could occur during any stage of RIG administration.

Since the introduction of the current recommendations, the amount of RIG to administer is estimated to be on average 40% of the quantity that was previously required based on body weight alone (*16*, *18*, *19*). Hence, these recommendations are expected to have a net positive effect on the cost of human rabies prophylaxis for patients and governments.

Costs/cost–effectiveness

In general, all RIGs are relatively expensive and not readily available. The cost per dose of eRIG is reported to range between US$ 25 and US$ 50, while the cost per dose of hRIG is between US$ 100 and US$ 250 (*20*).

For example, in Cambodia, eRIG costs between US$ 20 and US$ 30 per dose. In comparison, a Cambodian farmer's monthly salary is between US$ 60 and US$ 80 (*21*). Thus, a dose of RIG can consume up to half a month's salary. The high cost of RIG compared with income also exists throughout Africa and Asia (*5*, *21*, *22*). This difference is even wider for hRIG, and thus it is impractical for use in areas with limited financial resources (*23*).

Based on available data and experience of use for postexposure prophylaxis, eRIG is considered to be a safe and effective alternative in the many areas where hRIG is unavailable or unaffordable (*24*, *25*).

Availability

Currently, eRIG has regulatory approval mostly in less developed countries in Africa, Asia and Central and South America, and in other countries including Brazil, China, India and Thailand. Availability is irregular, and depends in part on equine stocks, local animal welfare concerns and production limitations.

Other considerations

Not applicable

Committee recommendations

The Expert Committee acknowledged the public health need for effective interventions for rabies postexposure prophylaxis, noting that the case fatality of rabies infection is almost 100% after the onset of clinical symptoms and that access to rabies postexposure prophylaxis is still inadequate in many settings where rabies is endemic.

The Expert Committee noted that efficacy of eRIG is similar to hRIG and that adverse events are minimal with available purified eRIG preparations. The Expert Committee also noted that eRIG is recommended in WHO's 2018 rabies vaccine position paper approved by the Strategic Group of Experts on Immunization and that the price of eRIG is considerably lower than for hRIG.

Therefore, the Expert Committee recommended that purified eRIG be included on the core list of the EML and EMLc for use as part of rabies

postexposure prophylaxis, in line with WHO recommendations and based on a favourable benefit-to-harm ratio. The Committee considered that eRIG will provide a valuable alternative option to hRIG, at a lower cost, and increase procurement options.

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Section 22: MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

22.1 Contraceptives

22.1.6 Intravaginal contraceptives

Ethinylestradiol + etonogestrel – new formulation – EML

Ethinylestradiol + etonogestrel **ATC Code: G02BB01**

Proposal

Inclusion of ethinylestradiol + etonogestrel contraceptive vaginal ring to the core list of the EML.

Applicant

Chemo Ibérica S.A., Madrid, Spain

WHO technical department

Sexual and Reproductive Health and Research

EML/EMLc

EML

Section

22.1.6 Intravaginal contraceptives

Dose form(s) & strength(s)

Vaginal ring: 2.7 mg + 11.7 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Ethinylestradiol + etonogestrel contraceptive vaginal ring has not previously been considered by the Expert Committee for inclusion on the Model List.

Ethinylestradiol is included on the EML as a component of combined oral contraceptives. Etonogestrel is included on the EML in an implantable contraceptive rod formulation.

In 2015, the Expert Committee recognized that many factors can influence a person's choice and use of contraception, including cultural and religious values, individual preferences, medical conditions, delivery methods, cost and convenience. The Committee strongly supported the principle of choice for people in the provision of family planning and contraception (*1*).

Public health relevance (burden of disease)

Unintended pregnancy is well recognized as a serious public health issue both in developed and developing countries. Even though the rate of unintended pregnancy has declined globally in the past decade, it remains high, particularly in low- and middle-income countries (*2*). Unintended pregnancy is associated with adverse physical, mental, social and economic outcomes, and contributes to both maternal and infant mortality (*3*).

Modern methods of contraception have a vital role in preventing unintended pregnancies. Among women who experienced an unintended pregnancy leading to an abortion, half had discontinued their contraceptive method for reasons related to the method such as health concerns, side-effects or inconvenience of use (*4*).

Target 3.7 of the Sustainable Development Goals (SDGs) is to ensure, by 2030, universal access to sexual and reproductive health care services, and the integration of reproductive health into national strategies and programmes (*5*).

Summary of evidence: benefits (from the application)

The contraceptive efficacy of ethinylestradiol + etonogestrel vaginal ring was evaluated in two open-label, non-comparative studies in Europe and North America involving 2322 women for 23 298 cycles, equivalent to 1786 women years (intention-to-treat population) (*6*, *7*). From the pooled results of the two studies, 21 pregnancies occurred during the study period, giving a pearl index (contraceptive failures per 100 women years) of 1.18 (95% confidence interval (CI) 0.73 to 1.80). Eleven of the pregnancies were attributable to non-compliance; the pearl index for the women in the per-protocol group was 0.77 (95% CI 0.37 to 1.40) (*8*).

The comparative efficacy of ethinylestradiol + etonogestrel vaginal ring versus ethinylestradiol + levonorgestrel combined oral contraceptive was evaluated in a phase III, open-label, multicentre randomized trial of 1030 women, conducted in nine European and two South American countries (*9*). Ten pregnancies occurred during treatment in the intention-to-treat population, five in each treatment arm. Five pregnancies occurred in the per-protocol population, three in the vaginal ring arm and two in the combined oral contraceptive arm. No significant differences were seen in contraceptive efficacy between treatment groups. Pearl indices for the intention-to-treat populations

for the vaginal ring and combined oral contraceptive groups were 1.23 (95% CI 0.40 to 2.86) and 1.19 (95% CI: 0.39 to 2.79), respectively. For the intention-to-treat population, the cumulative probability of in-treatment pregnancy was 1.20% (95% CI 0.14 to 2.26%) and 1.07% (95% CI 0.13 to 2.00%), for the vaginal ring and combined oral contraceptive groups, respectively. For the per-protocol population, the estimated probabilities of pregnancy were 0.71% (95% CI 0.00 to 1.52%) for the vaginal ring group and 0.43% (95% CI 0.00 to 1.01%) for the combined oral contraceptive group.

Similar results were observed in another open-label, multicentre randomized controlled trial involving 983 women in 10 European countries that compared ethinylestradiol + etonogestrel vaginal ring with a combined oral contraceptive containing ethinylestradiol + drospirenone (*10*). Five pregnancies occurred during the study, one in the vaginal ring group and four in the combined oral contraceptive group. Pearl indices for the intention-to-treat population were not significantly different between treatment groups: 0.25 (95% CI 0.01 to 1.36) for the vaginal ring group and 0.99 (95% CI 0.27 to 2.53) for the combined oral contraceptive group.

An open-label, prospective, single-arm, non-randomized study assessed real-life use of the ethinylestradiol + etonogestrel vaginal ring over three cycles in 252 women in India (*11*). No pregnancies were reported during the study period.

Three postmarketing observational studies in Germany (*12*), the Netherlands (*13*) and Switzerland (*14*) support the contraceptive efficacy findings of the clinical trials.

Good user and partner acceptability of the vaginal ring has been reported in several studies (*6*, *7*, *10*, *11*, *15*, *16*).

Summary of evidence: harms (from the application)

In the two non-comparative studies of contraceptives (*6*, *7*), 65.5% of participants reported at least one adverse event, of which 37.5% were considered to be possibly, probably or definitely treatment-related; 15.1% of participants discontinued the contraceptive due to adverse events. The most commonly reported treatment-related adverse events were headache (5.8%), vaginitis (5.6%), vaginal discharge (4.8%) and device-related events (foreign body sensation, sexual problems and expulsion (4.4%). The most common adverse events leading to treatment discontinuation were device-related events, headache, emotional lability and weight gain. Over the study period, mean weight gain was less than 1 kg from baseline. No clinically relevant changes in systolic or diastolic blood pressure were reported (*6*).

The most commonly reported treatment-related adverse events in both arms of the comparative trials were headache, vaginitis, method-related events,

vaginal discharge, breast pain and nausea, which occurred more frequently in the vaginal ring treatment arms (*9*, *10*).

Additional evidence (not in the application)

A Cochrane systematic review compared contraceptive effectiveness, cycle control, patient adherence and safety of combined hormonal contraceptives in transdermal patch and vaginal ring formulations versus combined oral contraceptives (*17*). The review included 11 randomized controlled trials that compared ethinylestradiol + etonogestrel vaginal contraceptive ring with combined oral contraceptives. No significant difference between treatment methods was observed for contraceptive effectiveness. Women using the vaginal ring generally had fewer adverse events than oral contraceptive users – less nausea, acne, irritability, depression and emotional liability – but they experienced more vaginal irritation and discharge. The incidence of deep vein thrombosis among users of the vaginal ring was estimated to be 149 per 100 000 women years (95% CI 18 to 538), based on two events. The authors stated that due to the rarity of events reported, these trials do not provide adequate evidence on the comparative risk of deep vein thrombosis.

A second systematic review of 14 randomized controlled trials also compared the efficacy and side-effects of the vaginal ring versus combined oral contraceptives (*18*). This review found a trend towards higher efficacy for the vaginal ring for preventing pregnancy (Peto odds ratio (OR) 0.52, 95% CI 0.26 to 1.04), as well as significantly less nausea and breakthrough bleeding reported (Peto OR for nausea 0.66 95% CI 0.49 to 0.99; Peto OR for breakthrough bleeding 0.68, 95% CI 0.51 to 0.91). No significant differences were found between contraceptive methods in measures of compliance.

WHO guidelines

The WHO *Medical eligibility criteria for contraceptive use* (*19*) notes that based on the available evidence, the combined contraceptive vaginal ring has a comparable safety and pharmacokinetic profile and has similar effects on ovarian function to combined oral contraceptives with similar hormone formulations in healthy women. Weight gain did not differ between vaginal ring users and combined oral contraceptive users who had a body mass index ≥ 30 kg/m^2.

Limited evidence on use by women after medical and surgical abortion found no serious adverse events and no infection related to use during three cycles of follow-up after abortion. In addition, in women with low-grade squamous intraepithelial lesions, use of the vaginal ring did not worsen the condition.

Pending further evidence, the guideline development group concluded that the evidence available for combined oral contraceptives applies also to the

combined contraceptive vaginal ring. Therefore, the combined contraceptive vaginal ring should have the same categories for use as combined oral contraceptives.

Costs/cost–effectiveness

The cost–effectiveness of contraception for preventing unintended pregnancy is widely recognized (*20*).

The application described a study that assessed the cost–effectiveness of different combined hormonal contraceptive methods in Spain (*21*). This study used a Markov model of three methods: reimbursed oral contraceptive, contraceptive patch and vaginal ring. The most cost-effective method from the perspective of the National Health Service was the vaginal ring. However, the vaginal ring was the most expensive method for patients.

Availability

Nuvaring®, the innovator device developed by Organon (Merck), is registered in more than 50 countries. Generic brands are available.

The ethinylestradiol + etonogestrel vaginal ring manufactured by the applicant is registered in several European countries, including Belgium, Czechia, Denmark, Finland, France, Italy, the Netherlands, Poland, Portugal and Spain.

No information was presented on the availability of ethinylestradiol + etonogestrel vaginal ring in low- and middle-income settings.

Other considerations

Not applicable.

Committee recommendations

The Expert Committee noted target 3.7 of the SDGs to ensure universal access to sexual and reproductive health care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes by 2030.

The Committee acknowledged that effective contraception contributes to advancing maternal and child health, and reduces unintended pregnancies and the need for abortion (particularly unsafe abortion). Access to family planning reinforces people's rights to determine the number and spacing of their children. The Committee noted that the unmet need for contraception in many settings is high and is highest among the most vulnerable in society. The Committee agreed with the WHO Sexual and Reproductive Health and Research Department in supporting the principle of choice for people in the provision of family planning and contraception.

The Expert Committee noted that the available evidence supports the comparable effectiveness of the combined contraceptive vaginal ring to alternative hormonal contraceptive methods. It also noted that the contraceptive vaginal ring had a safety profile largely consistent with well-established safety profiles of other combined hormonal contraceptives, but had unique device-related effects (e.g. vaginitis and discharge).

The Committee noted that combined contraceptive vaginal rings are included in the WHO medical eligibility criteria for contraceptive use, and that the WHO technical department supported the inclusion of the ethinylestradiol + etonogestrel vaginal ring in the Model List.

The Committee noted that the ethinylestradiol + etonogestrel vaginal ring is widely available including in generic forms.

Based on the evidence for efficacy and safety, recommendations in WHO guidelines, and in line with the philosophy of offering multiple contraceptive choices for people seeking family planning and contraception, the Committee recommended inclusion of the ethinylestradiol + etonogestrel vaginal ring on the core list of the EML.

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22.5 Other medicines administered to the mother

Multiple micronutrient supplement – addition – EML

Multiple micronutrient supplements **ATC Code: A11AA04**

Proposal

Addition of multiple micronutrient supplements on the EML as an antenatal supplement for pregnant women.

Applicant

New York Academy of Sciences, New York, United States of America and the Micronutrient Forum

WHO technical department

Nutrition and Food Safety
Maternal, Newborn, Child & Adolescent Health & Ageing

EML/EMLc

EML

Section

22.5 Other medicines administered to the mother

Dose form(s) & strength(s)

Suggested components follow the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) formulation (*1*).

Tablet containing:

Component (chemical entity)	Amount
Vitamin A (retinol acetate)	800 micrograms retinol activity equivalent
Vitamin C (ascorbic acid)	70 mg
Vitamin D (cholecalciferol)	5 micrograms (200 IU)
Vitamin E (alpha tocopherol succinate)	10 mg alpha tocopherol equivalent
Vitamin B1 (thiamine mononitrate)	1.4 mg
Vitamin B2 (riboflavin)	1.4 mg
Vitamin B3 (niacinamide)	18 mg niacin equivalent

Table *continued*

Component (chemical entity)	Amount
Vitamin B6 (pyridoxine hydrochloride)	1.9 mg
Folic acid (folic acid)	680 micrograms dietary folate equivalent (400 micrograms)
Vitamin B12 (cyanocobalamin)	2.6 micrograms
Iron (ferrous fumarate)	30 mg
Iodine (potassium iodide)	150 micrograms
Zinc (zinc oxide)	15 mg
Selenium (sodium selenite)	65 micrograms
Copper (cupric oxide)	2 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Multiple micronutrient supplements for use as an antenatal supplement for pregnant women have not previously been considered for inclusion on the EML.

Public health relevance (burden of disease)

Sufficient intake of micronutrients are required during pregnancy to support maternal health and normal fetal development (*2*). Globally, many pregnant women do not meet these requirements, which has negative consequences for their own health as well as for the health, growth and development of their infants. Insufficient nutrient intake before and during pregnancy, combined with increased metabolic demands during pregnancy, results in severe nutritional deficiencies, particularly in low- and middle-income countries where many women enter pregnancy already malnourished.

Maternal anaemia is the most common micronutrient deficiency, affecting 40% of pregnant women globally. In the WHO regions, South-East Asia (49%), Africa (46%) and the Eastern Mediterranean (41%) have the highest prevalence followed by Western Pacific (33%), the Americas (26%) and Europe (27%) (*3*). While anaemia is not always due to iron deficiency, a 2013 analysis suggested that 19.2% of pregnant women in low- and middle-income countries had iron deficiency anaemia (*4*).

A literature review of micronutrient deficiencies found that vitamin D, iodine and zinc deficiencies were widespread in women of reproductive age. On average in low- and middle-income countries, 63.2% of women of reproductive age were vitamin D deficient, 41.4% were zinc deficient, 31.2% were anaemic, 22.7% were folate deficient and 15.9% were vitamin A deficient, using WHO cut-off criteria for each indicator (*5*).

Adverse pregnancy outcomes, including low birth weight (LBW), small for gestational age, preterm birth and perinatal mortality, are relatively common in low- and middle-income countries, and are associated with micronutrient deficiencies. Overall, 14.6% of all live births in low- and middle-income countries in 2015 were LBW (< 2500 g) with South Asia having the greatest burden (26.4%) (*6*). Babies that are preterm or small for gestational age have an increased mortality risk (7). On the basis of secondary analyses of data from the 2012 Child Health Epidemiology Reference Group in low- and middle-income countries, an estimated 23.3 million infants, or 19.3% of all live births, were small for gestational age, and an estimated 606 500 neonatal deaths (21.9% of all neonatal deaths) were attributable to being small for gestational age. Infants that are small for gestational age are defined as those weighing < 10th centile of birth weight-for-gestational age and sex according to the multiethnic, INTERGROWTH-21st birth weight standard (*8*). South Asia also had the highest prevalence of infants born small for gestational age (34% of all live births).

A 2018 review assessing data from national registries, reproductive health surveys and published studies estimated that 14.84 million children, or 10.6% of live births, were born preterm worldwide in 2014. More than 80% of preterm babies were born in Asia (7.8 million or 10.4% of live births) and sub-Saharan Africa (4.2 million or 12.0% of live births) (*9*). Global estimates for stillbirths and neonatal mortality are 18.4 per 1000 total births and 18.6 per 1000 live births, respectively, with regionally higher prevalence in sub-Saharan Africa and South Asia (*10*, *11*).

Summary of evidence: benefits (from the application)

To date, 21 clinical trials have compared the use of multiple micronutrient supplements with iron and folic acid supplements in pregnant women in low- and middle-income countries, and 10 of these trials used the UNIMMAP formulation. Two meta-analyses compared multiple micronutrient supplements with iron and folic acid supplements from trial data, including a 2019 Cochrane review that included 19 trials (*12*) and a 2017 individual patient data meta-analysis of 17 trials (*13*).

The Cochrane review showed that, overall, multiple micronutrient supplements resulted in a 12% reduction in low birth weight (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.85 to 0.91) and an 8% reduction in births

of babies that were small for gestational age (RR 0.92, 95% CI 0.88 to 0.97) compared with iron and folic acid supplementation, with high and moderate quality evidence (based on GRADE criteria), respectively (*12*). No significant differences were found for other maternal or pregnancy outcomes assessed, including preterm birth, stillbirth, maternal anaemia in the third trimester, miscarriage, maternal mortality, perinatal mortality, neonatal mortality or risk of delivery by caesarean section, when multiple micronutrient supplements were compared with supplementation with iron with or without folic acid.

The Cochrane review included several population-level subgroup analyses, including analyses that stratified based on the study-specific averages of maternal body mass index, maternal height, timing of supplementation and iron dose (*12*). Based on the 10 trials in which the average maternal body mass index was ≥ 20 kg/m², there was evidence of a lower incidence of babies born small for gestational age among women who received multiple micronutrient supplements compared with those who received iron and folic acid supplementation ($P = 0.001$). However, there was no evidence of a difference based on the three trials where the mean body mass index was < 20 kg/m². Similarly, based on the six trials in which the average maternal height was ≥ 154.9 cm, multiple micronutrient supplementation was associated with a reduction in babies born small for gestational age compared with those who received iron and folic acid supplementation ($P < 0.001$), while no effect was seen in the eight trials in which the average maternal height was < 154.9 cm. Thus, while the review suggests that multiple micronutrient supplements reduce the risk of babies born small for gestational age, this effect was only seen in women with better nutritional status, as defined by a height of at least 154.9 cm or a body mass index of at least 20 kg/m². Based on trials in which the average maternal body mass index was < 20 kg/m², women receiving multiple micronutrient supplements had a lower rate of preterm birth compared with those who received iron and folic acid supplementation ($P < 0.001$), whereas no difference for preterm birth was observed among trials in which the average body mass index was ≥ 20 kg/m². No statistically significant subgroup differences were found by the dose of iron for preterm birth, small for gestational age birth or perinatal mortality based on 15 studies included in this subgroup analysis.

The 2017 individual patient data meta-analysis found that multiple micronutrient supplements reduce the risk of stillbirth (on the basis of fixed-effects analysis), very low birth weight, low birth weight, early preterm birth, preterm birth and small for gestational age birth (by the standards of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) and Oken reference) compared with iron and folic acid supplementation (*13*). This analysis also found an increased risk of being born large for gestational age (by INTERGROWTH-21st standards but not by

Oken reference) in women taking multiple micronutrient supplements. While this finding may raise concerns about increased risk of obstructed labour and/or asphyxiation, the authors noted that multiple micronutrient supplementation was not associated with increased risk of stillbirth or mortality at any time point, including among women with short stature (< 150 cm), who are more likely to be at risk of obstructed labour.

Twenty-six subgroup analyses were conducted with numerous outcomes to identify individual characteristics that may modify the effect of multiple micronutrient supplementation compared with iron and folic acid supplementation alone. Subgroup analyses found that the beneficial effects of multiple micronutrient supplementation compared with iron and folic acid supplementation were greater in anaemic pregnant women than non-anaemic pregnant women for low birth weight (19% reduction versus 9% reduction), small for gestational age births (8% reduction versus 1%) and 6-month infant mortality (29% reduction versus 7% reduction). The effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing the risk of preterm birth were greater in underweight pregnant women than non-underweight women (16% reduction versus 6% reduction).

The effects of maternal multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing mortality were greater in female infants than male infants for neonatal mortality (15% reduction versus 6% increase), 6-month mortality (15% reduction versus 2% reduction) and infant mortality (13% reduction versus 5% increase).

The effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing the risk of preterm birth were greater in women who started supplementation before 20 weeks of gestation than those who started after 20 weeks (11% reduction versus no change after 20 weeks). However, the effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing the risk of stillbirth were greater in women who started supplementation after 20 weeks of gestation than those who started before 20 weeks (19% reduction versus 3% reduction).

The effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing mortality were greater when adherence was ≥ 95% versus < 95% for neonatal mortality (12% reduction versus 5% increase) and infant mortality (15% reduction versus 6% increase).

Multiple micronutrient supplementation did not have any significant effect on the risk of stillbirth, or neonatal, 6-month or infant mortality in any of the 26 subgroups analysed compared with iron and folic acid supplementation.

Summary of evidence: harms (from the application)

The Cochrane review found no harms for multiple micronutrient supplementation in terms of mortality outcomes (stillbirths, perinatal and neonatal mortality) (*12*). This conclusion was supported by two trials that were statistically powered to analyse the effect on early infant mortality. A large trial in Bangladesh did not find an increase in neonatal or early infant mortality risk in the multiple micronutrient supplementation group versus the control (iron and folic acid supplementation). In a posthoc analysis, however, higher neonatal mortality was reported in male infants due to birth asphyxia (*14*). The Cochrane review authors concluded that these findings should be interpreted with caution due to potential misclassification of the underlying cause of death, which was ascertained by verbal autopsy with parents (*12*).

A recent analysis examined the risk of exceeding the upper intake level, as set by the United States National Academy of Medicine, of any micronutrient in the UNIMMAP formulation if it is consumed with a nutritionally adequate diet (*15*). In this case, most of the micronutrient intakes remain well below the upper level and only iron, folic acid and niacin would meet or slightly exceed the upper level.

For niacin, the upper level is based on the side-effect of flushing and only occurs with the synthetic form nicotinic acid, which is not used in dietary supplements. UNIMMAP contains 18 mg of nicotinamide (not nicotinic acid) so this does not contribute to the upper intake level. If niacin were present in the form of nicotinic acid, it would still be well below the upper intake level of 35 mg/day (*15*).

For folic acid, there are no known side-effects for reaching the upper level. Rather, the upper level is set based on the risk of masking the diagnosis of pernicious anaemia, which can occur with high folate intake in the presence of vitamin B12 deficiency. However, multiple micronutrient supplementation contains vitamin B12, which reduces this risk (*15*).

The National Academy of Medicine gives the upper level for iron as 45 mg/day based on gastrointestinal side-effects which are most commonly reported when a supplement is taken on an empty stomach and would be a concern for both multiple micronutrient supplementation and iron and folic acid supplementation. WHO recommends pregnant women receive between 30 mg and 60 mg of iron a day (*16*), which is met by the UNIMMAP formulation. Importantly, the upper levels are set for the healthy population and do not apply to the treatment of iron deficiency anaemia in which case the daily iron intake may need to exceed the upper level (*15*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

The 2020 *WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: multiple micronutrient supplements during pregnancy* (*16*), recommend antenatal multiple micronutrient supplementation only "in the context of rigorous research". This recommendation updates the 2016 guidelines (*17*), when antenatal multiple micronutrient supplementation was not recommended . The recommendation was changed because, while the evidence suggests that there may be a limited benefit and little harm in replacing iron and folic acid supplements with multiple micronutrient supplements, the evidence on low birth weight and its component parts (preterm birth and small for gestational age birth) was difficult to interpret. Gestational age accurately assessed by ultrasound emerged as an important feature of future trials. In addition, the sustainability of changing to the higher-cost multiple micronutrient supplements is not known and more evidence is needed on the effects of changing to a 30 mg dose of iron from a higher dose of iron (e.g. 60 mg), particularly in settings where higher doses of iron are routinely used due to a high prevalence of anaemia or other reasons.

The 2013 WHO guidelines for nutritional care and support for patients with tuberculosis (*18*) recommend that all pregnant women with active tuberculosis receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals, according to the UNIMMAP, to complement their maternal micronutrient needs (conditional recommendation, very low quality evidence).

Multiple micronutrient supplementation has also been recommended by WHO, UNICEF and the World Food Programme for pregnant women affected by an emergency (*19*).

Costs/cost–effectiveness

The current listed price of the multiple micronutrient supplements provided by the UNICEF Supply Catalogue website is US$ 1.79 for 100 tablets (product no. S1580101) (*20*). To provide 6-month coverage per individual, the unit cost adjusted to 180 tablets is US$ 3.22. Depending on the packaging and other variables, the price can vary considerably, but based on information from global manufacturers and UNICEF, the median price for a 180-tablet bottle is US$ 2.50 for a purchase at scale.

The cost of the supplements is important to know as well as the programme implementation costs, including national-level administration, training, nutrition education programmes and supervision. The estimated programmatic roll-out cost is US$ 0.42 per patient, using a published calculation methodology (*21*).

Several recent studies have shown the cost–effectiveness of multiple micronutrient supplementation compared to iron and folic acid supplementation.

A 2019 analysis modelled the cost–effectiveness of the two interventions in Pakistan, India and Bangladesh (*22*). The analysis found that multiple micronutrient supplementation would avert 4391, 5769 and 8578 more disability-adjusted life years (DALYs) than iron and folic acid supplementation per 100 000 pregnancies in Pakistan, India and Bangladesh, respectively (62.6%, 76.8%, and 82.6% certainty). The incremental cost–effectiveness ratio of transitioning from iron and folic acid supplementation to multiple micronutrient supplementation was US$ 41.54, US$ 31.62 and US$ 21.26 per DALY averted, for Pakistan, India and Bangladesh, respectively. This study concluded that multiple micronutrient supplementation was cost-effective and resulted in positive health outcomes for both infants and pregnant women, and supports the transition from iron and folic acid supplementation to multiple micronutrient supplementation in Pakistan, India, and Bangladesh. This modelling was subsequently done for 29 additional countries, which found multiple micronutrient supplementation was highly cost-effective in all scenarios modelled (*23*).

Another 2019 modelling analysis that evaluated the cost–effectiveness of transitioning from iron and folic acid supplementation to multiple micronutrient supplementation focused on Bangladesh and Burkina Faso (*24*). The analysis found that transitioning to multiple micronutrient supplementation could avert more than 15 000 deaths and 30 000 cases of preterm birth annually in Bangladesh (compared with iron and folic acid supplementation) and more than 5000 deaths and 5000 cases of preterm births in Burkina Faso. The cost per death averted was US$ 175–185 in Bangladesh and US$ 112–125 in Burkina Faso.

Availability

Antenatal micronutrient supplements, with similar formulations to UNIMMAP, which provide about 1 recommended dietary allowance (RDA) a day of approximately 15 micronutrients, are widely available in pharmacies and other market places globally. A market assessment of 32 low- and middle-income countries found that every country had either locally manufactured or imported maternal multiple micronutrient supplementation products containing at least 10 micronutrients (*25*). While none of the multiple micronutrient supplementation products matched the UNIMMAP formulation, the wide availability of multiple micronutrient formulations indicates that there is global manufacturing capacity that could meet the global need for a UNIMMAP-multiple micronutrient supplementation product.

As with most nutrition supplements, no global consensus exists on the regulatory status of the multiple micronutrient supplementation product for pregnant women. At the individual country-level, this product can be considered either as a dietary supplement and regulated as a food, or as a therapeutic product that is regulated as a drug. In some countries, including the India, Japan, USA, and European Union countries, multiple micronutrient supplements are

regulated as a dietary supplement, while in other countries, such as Australia, Bangladesh, Mexico and New Zealand, multiple micronutrient supplements are regulated as a drug. The regulatory classification of multiple micronutrient supplements can have implications for how the product is manufactured, imported, packaged, distributed and/or promoted. To help establish a product that conforms to internationally recognized good manufacturing practice (GMP) requirements and pharmacopoeial standards, the *Expert consensus UNIMMAP – MMS product specification* was created by an expert panel hosted jointly by the New York Academy of Sciences and the Micronutrient Forum (*26*). Manufacturers of supplements must be registered entities and certified as adhering to GMP requirements. For GMP, these include the requirements of the Australian Therapeutics Goods Administration, Health Canada, US Food and Drug Administration, or the WHO for the manufacture of nutritional products. For pharmacopoeias, these include quality standards for nutritional supplements as set by the British Pharmacopeia, European Pharmacopeia, International Pharmacopeia, Japanese Pharmacopeia and US Pharmacopeia.

Currently, four companies manufacture a UNIMMAP-formulated product for global distribution: Contract Pharmacal Corporation, DSM Nutritional Products, Lekapharm and Lomapharm. In addition, there are companies manufacturing a multiple micronutrient supplementation product for local distribution, such as Beximco and Renata in Bangladesh. The Renata product will conform to the *Expert consensus UNIMMAP – MMS product specification*.

Other considerations

The Committee noted the many letters of support received in relation to this application.

Committee recommendations

The Expert Committee noted the high prevalence of nutritional deficiencies in low- and middle-income countries where many women enter pregnancy already malnourished. Deficiencies of multiple essential vitamins and minerals result in potentially severe health consequences for pregnant women and their infants, including increased maternal and perinatal mortality.

The Committee noted that evidence from over 20 randomized trials conducted across multiple countries, often at low risk of bias, demonstrates that daily supplementation with multiple micronutrient supplements in pregnancy compared with supplementation with iron and folic acid alone improves pregnancy outcomes. While the evidence does not show benefits in terms of neonatal and maternal mortality, it does show a relevant reduction in the risk of small for gestational age births, low birth weight and preterm and very preterm births. Data on mortality are affected by the high heterogeneity among studies.

The evidence also shows that multiple micronutrient supplements are safe and cost-effective compared with iron and folic acid supplements, particularly where the prevalence of undernourished women is high.

The Committee noted recommendations about use of multiple micronutrient supplements in pregnant women included in WHO guidelines, and joint WHO, UNICEF and World Food Programme guidelines. All recommendations agree on the direction of the recommendation (i.e. recommending multiple micronutrient supplements in certain situations), despite differences in terms of the strength and scope of the recommendations at the population level (e.g. restriction to emergency settings, use in women with tuberculosis or use in the context of research). The Committee agreed that more research is needed on the effects of switching from daily iron and folic acid supplements containing a 60 mg dose of elemental iron to daily multiple micronutrient supplements containing a lower dose (30 mg) of elemental iron in populations with a high prevalence of iron deficiency anaemia, but also recognized that there is no evidence of harm in this group. The Committee considered, however, that listing multiple micronutrient supplements as an essential medicine would not prevent answering this important question and similar questions (e.g. the potential interactions between different micronutrients) and may facilitate research.

The Committee also expressed reservations about the probability that new trials will be started and completed in the short term to further explore the benefits and harms of multiple micronutrient supplements or their acceptability compared with tablets with a smaller number of micronutrients. Implementation research on the adoption of multiple micronutrient supplements will be informative, but it is unlikely that this evidence will change the cumulative evidence reached so far, with a benefit-to-harm ratio clearly in favour of multiple micronutrient supplements.

The Committee therefore recommended listing multiple micronutrient supplements on the core list of the EML for the use as an antenatal supplement in pregnant women. The Committee considered that further evidence on the adequacy of the daily elemental iron dose in multiple micronutrient supplements is desirable.

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Section 24: MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

Methylphenidate – addition – EML and EMLc

Methylphenidate hydrochloride **ATC Code: N06BA04**

Proposal

Addition of methylphenidate to the EML and EMLc for the treatment of attention-deficit/hyperactivity disorder (ADHD).

Applicant

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WHO technical department

Comments on the application were provided by the WHO Department of Mental Health and Substance Use. The technical department advised that the guidelines of the Mental Health Gap Action Programme (mhGAP) include the use of methylphenidate in the management of children at least 6 years old with a diagnosis of ADHD. Methylphenidate is provided as second-line treatment (after parent training and behavioural interventions) and must be initiated by a specialist. The mhGAP guideline update process is underway and this recommendation will be examined to consider if it needs to be modified.

Important considerations for the Expert Committee were highlighted relating to health systems capacity to enforce and implement protocols for ADHD diagnosis, to prescribe and initiate methylphenidate treatment, and to ensure careful clinical monitoring for side-effects, clinical response, adherence, treatment acceptability and dose adjustment. The risks of methylphenidate misuse, overmedicalization and overtreatment of behavioural problems in children will also be considered.

EML/EMLc

EML and EMLc

Section

24 Medicines used in behavioural disorders

Dose form(s) & strength(s)

Tablet (immediate-release): 5 mg; 10 mg; 20 mg
Tablet (immediate-release, chewable): 2.5 mg; 5 mg; 10 mg
Tablet (orally dispersible): 8.6 mg; 17.3 mg; 25.9 mg
Oral solution (short-acting): 5 mg/5 mL; 10 mg/5 mL

Oral solution (extended-release): 25 mg/5 mL
Solid-oral dosage form (extended-release): multiple strengths ranging from 10 mg to 100 mg
Transdermal patch: 1.1 mg; 1.6 mg; 2.2 mg; 3.3 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

An application for the inclusion of methylphenidate on the EML and EMLc for the treatment of ADHD was considered by the Expert Committee in 2019. Listing was not recommended due to concerns about the quality and interpretation of the evidence for benefits and harms (*1*).

Public health relevance (burden of disease)

In 2019, the global prevalence of ADHD was estimated to be 2.6% of children and adolescents aged 5 to 19 years; within this age group, ADHD accounted for 0.29% of total global disability-adjusted life years (DALYs) (*2*).

Studies and meta-analyses have shown ADHD to be associated impairment of quality of life (*3*, *4*), social and emotional impairment (*5–8*), greater risk of accidental injuries (*9–15*), greater risk of premature death and suicide (*16–21*), increased crime and delinquency (*22–26*), educational underachievement (*27–29*), substance use disorders (*30–32*) and increased economic burden for individuals, families and society (*33–42*).

Summary of evidence: benefits (from the application)

The current application represented much of the same evidence included in the 2019 application. The new evidence included in the current application is summarized below.

Evidence for short-term efficacy from randomized controlled trials

A 2018 systematic review and network meta-analysis evaluated the comparative efficacy of oral medications for ADHD, including methylphenidate, versus each other or placebo (*43*). It comprised 133 randomized controlled trials, including 81 trials in children and adolescents, 51 in adults and one in both. A total of 14 346 children and adolescents were included in the efficacy analysis. The overall risk of bias was rated as low in 23.5% of the studies included, unclear in 65.4%, and high in 11.1%.

The primary efficacy outcome was measured as change in severity of ADHD core symptoms based on teachers' and clinicians' ratings, at time points closest to 12 weeks of treatment. In children and adolescents, methylphenidate was superior to placebo with respect to ADHD core symptoms rated by both clinicians (standard mean difference (SMD) –0.78, 95% CI –0.93 to –0.62) and teachers (SMD –0.82, 95% CI –1.16 to –0.37). The quality of the evidence from randomized controlled trials in children and adolescents for the comparison of methylphenidate versus placebo was rated as low for teachers' ratings (five studies) and moderate for clinicians' ratings (five studies).

Evidence for longer-term effectiveness from observational studies

A qualitative systematic review of 40 observational studies from 2008 to 2019 investigated the effects of ADHD medication on behavioural and neuropsychiatric outcomes using linked prescription databases. It included 18 studies that used within-individual designs to account for confounding by indication (*44*). These studies found short-term beneficial effects of ADHD medication (not limited to methylphenidate) for outcomes such as injuries, motor vehicle accidents, substance use disorder and education, with estimates of relative reduction ranging from 9% to 58%. The within-individual studies found no evidence of increased risks of suicidality and seizures. Most of the within-individual studies included in the systematic review were short-term studies. The authors concluded that the available evidence from pharmacoepidemiological studies on long-term effects of ADHD medication were less clear.

Summary of evidence: harms (from the application)

The most common adverse effects of methylphenidate are loss of appetite and insomnia. Other common adverse effects include erythema, headache, mild labile mood, nasal congestion, nasopharyngitis, nausea, vomiting and weight loss (*45–48*).

A 2018 systematic review and network meta-analysis evaluated the tolerability of medications, including methylphenidate, for ADHD in children, adolescents and adults (*43*). Tolerability was measured as the proportion of patients who dropped out of studies because of side-effects. The review included 82 trials (11 018 children and adolescents) in the tolerability analysis. The tolerability of methylphenidate was not significantly different from placebo (odds ratio (OR) 1.44, 95% CI 0.90 to 2.31). In children and adolescents, compared with placebo, the use of methylphenidate was associated with significantly increased diastolic blood pressure (SMD 0.24, 95% CI 0.14 to 0.33) and decreased weight (SMD –0.77, 95% CI –1.09 to –0.45). There was no significant increase in systolic blood pressure (SMD 0.09, 95% CI –0.01 to 0.19).

A 2015 Cochrane systematic review of randomized clinical trials of methylphenidate in children and adolescents with ADHD found no increase in

serious adverse events, but a high proportion of participants suffered a range of non-serious adverse events (*49*). A 2018 Cochrane systematic review of 260 non-randomized studies evaluated adverse events of methylphenidate in children and adolescents with ADHD (*50*). Among other findings, the review found very low quality evidence that methylphenidate increased the risk of serious adverse events (risk ratio (RR) 1.36, 95% CI 1.17 to 1.57; two studies, 72 005 participants); any psychotic disorder (RR 1.36, 95% CI 1.17 to 1.57; one study, 71 771 participants); and arrhythmia (RR 1.61, 95% CI 1.48 to 1.74; one study, 1224 participants). In contrast, two large population-based cohort studies using within-person designs found no evidence that methylphenidate was associated with psychotic disorders (*51*, *52*).

A 2020 meta-review of network meta-analyses, meta-analyses of randomized controlled trials, individual randomized controlled trials, and cohort studies reported 78 adverse effects across 80 psychotropic medications in 337 686 children and adolescents with mental disorders (53). It reported that, compared with placebo, methylphenidate was associated with significantly worse anorexia (RR 3.21, 95% CI 2.61 to 3.94), insomnia (OR 4.66, 95% CI 1.99 to 10.9), weight loss (SMD –0.77, 95% CI –1.09 to –0.45), nausea (RR 1.38, 95% CI 1.04 to 1.84) and abdominal pain (RR 1.50, CI 1.26 to 1.79).

Adverse effects of methylphenidate reported in observational studies include effects on height and weight (*54*, *55*), cardiovascular events (*56–58*), and cardiac malformations in infants born to women treated with methylphenidate during pregnancy (*59*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

The 2016 WHO mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings (version 2.0) (*60*) makes the following recommendations for the management of ADHD.

- Provide guidance on child/adolescent well-being.
- Provide psychoeducation to person and carers and parenting advice. Provide guidance on improving behaviour.
- Assess for and manage stressors, reduce stress and strengthen social support.
- Provide carer support.
- Liaise with teachers and other school staff.
- Link with other available resources in the community.
- Consider parent skills training when available.

- Consider behavioural interventions when available.
- If above treatments have failed AND the child/adolescent has a diagnosis of ADHD AND is at least 6 years old, refer to a specialist for methylphenidate treatment.
- Ensure appropriate follow-up every 3 months or more, if needed.

Costs/cost–effectiveness

The current application identified no new evidence on the cost–effectiveness of methylphenidate since the 2019 application. In 2019, the Expert Committee acknowledged that methylphenidate appeared to be low cost and affordable, but considered that no conclusions could be drawn on the cost–effectiveness of the medicine given the considerable uncertainty in the estimates of benefits and harms (*1*).

Availability

Methylphenidate, in various formulations and strengths, is available globally in originator and generic brands.

Other considerations

Non-medical use and diversion

A 2020 systematic review of the literature on the non-medical use and diversion of prescription stimulants (111 studies) found that non-medical use and diversion are highly prevalent. Self-reported rates among population samples ranged from 2.1% to 58.7% for non-medical use and from 0.7% to 80.0% for diversion. In most cases, non-medical use is associated with no, or minor, medical effects; however, adverse medical outcomes, including death, occur in some individuals, particularly when administered by non-oral routes. Methylphenidate should be used with caution or not at all in patients at risk of diversion or misuse (*61*).

Diagnosis

ADHD can only be diagnosed by a licensed clinician who interviews the parent or caregiver and/or patient to document criteria for the disorder. The condition cannot be diagnosed by rating scales alone, neuropsychological tests or methods for imaging the brain (*62–68*). The diagnosis requires: 1) the presence of developmentally inappropriate levels of hyperactive–impulsive and/or inattentive symptoms for at least 6 months; 2) symptoms occurring in different settings (e.g. home and school); 3) symptoms that cause impairment in living; 4) some of the symptoms and impairments first occurring in early to mid-childhood (before age 12 years); and 5) no other disorder better explains the symptoms (*62*, *68*, *69*).

Committee recommendations

The Expert Committee recalled the decision by the 2019 Expert Committee not to recommend methylphenidate for inclusion on the EML and EMLc for the treatment of ADHD due to concerns about the quality and interpretation of the evidence presented on benefits and harms.

The Committee considered the new evidence in the current application from a 2018 network meta-analysis of trials evaluating the comparative efficacy and tolerability of medications for ADHD, including but not limited to methylphenidate, in children, adolescents and adults. The Committee noted that most of the included studies in the network meta-analysis were judged to have an unclear or high risk of bias. In addition, few of the included studies measured outcomes beyond 12 weeks of treatment, which the Committee considered was a major limitation, given that ADHD is a longer-term condition.

With regard to safety and harms, the network meta-analysis reported on the outcome of tolerability, defined as the proportion of patients who dropped out of studies because of adverse effects. The Committee considered that this outcome did not provide adequate information on the frequency and severity of specific adverse effects associated with methylphenidate use. Known adverse effects of methylphenidate that require monitoring include effects on height velocity and weight, and cardiovascular effects such as changes in heart rate and blood pressure.

The Committee also considered that the true prevalence of ADHD was uncertain, because of variability in diagnostic approaches and the potential clinical overlap with other psychiatric illnesses. Given the potential for both under- and over-diagnosis, it is therefore difficult to estimate the actual burden of disease.

The Committee noted that the 2016 WHO mhGAP guidelines recommended that the use of stimulant medication must always be part of a comprehensive treatment plan that includes psychological, behavioural and educational interventions. Recommended first-line interventions for ADHD in the WHO mhGAP guidelines are non-pharmacological (environmental, behavioural and psychosocial). Referral to a specialist for consideration of methylphenidate is only recommended after non-pharmacological interventions have failed and the child is at least 6 years old. The Committee recognized that the availability of these recommended first-line interventions and specialists in the diagnosis and treatment of children with ADHD may be limited in many low- and middle-income countries. The Committee also noted advice from the WHO Department of Mental Health and Substance Use that the mhGAP guidelines are currently in the process of being reviewed and that the review process will take into consideration health systems capacity to: enforce and implement protocols for ADHD diagnosis; regulate the prescription and

initiation of methylphenidate treatment; and ensure careful clinical monitoring of adverse effects, clinical response, adherence, treatment acceptability, requirements for dose adjustment, and risk of misuse, overmedicalization and overtreatment of behavioural problems in children.

The Committee also noted with concern the high prevalence of non-medical use and diversion of prescription stimulants, including methylphenidate. The Committee noted that methylphenidate is included in the list of psychotropic substances under international control. As such, methylphenidate is subject to import and export restrictions and other legal mechanisms aimed at limiting its use only for scientific and medical purposes to prevent diversion and misuse.

Overall, the Committee considered that even with the new evidence presented in the application, together with previously considered data, the benefit-to-harm ratio for the long-term use of methylphenidate was still uncertain. The Committee therefore did not recommend the inclusion of methylphenidate on the EML and EMLc. The Committee advised that for any future consideration for the listing of methylphenidate, the following would be informative: evidence for the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings.

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24.1 Medicines used in psychotic disorders

Paliperidone and risperidone long-acting injection – addition – EML

Paliperidone	**ATC Code: N05AX13**
Risperidone	**ATC Code: N05AX08**

Proposal

Addition of paliperidone (1-month) and risperidone long-acting injection to the core list of the EML for maintenance treatment of adults with schizophrenia or related chronic psychotic disorders.

Applicant

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

WHO technical department

The Department of Mental Health and Substance Use provided comments on the application. It noted that the department had been approached on multiple occasions by various organizations (e.g. Médecins Sans Frontières, United Nations High Commissioner for Refugees and Christian Blind Mission) about the uncertainty of the future availability of fluphenazine, currently the only long-acting injectable antipsychotic on the EML. Long-acting injectable antipsychotic medicines are an established treatment option for schizophrenia and are recommended in existing guidelines of the WHO Mental Health Gap Action Programme (mhGAP).

The Department's comments also highlighted a recently published new systematic review by a different research group that showed significant benefits of long-acting injectable antipsychotic medicines versus oral antipsychotic medicines in preventing hospitalization or relapse (*1*), providing further evidence of the importance of having long-acting injectable antipsychotic medicines available in health services around the world.

EML/EMLc

EML

Section

24.1 Medicines used in psychotic disorders

Dose form(s) & strength(s)

Paliperidone: injection (prolonged-release) 25 mg, 50 mg, 75 mg, 100 mg, 150 mg (as palmitate)

Risperidone: injection (prolonged-release) 12.5 mg, 25 mg, 37.5 mg, 50 mg

Core/complementary

Core

Individual/square box listing

Individual listing for both paliperidone and risperidone

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Currently, the only long-acting injectable antipsychotic medicine included on the EML is fluphenazine (decanoate or enantate), with a square box as representative of unspecified alternatives within the same pharmacological class. The availability of fluphenazine globally is erratic, representing a major threat for people requiring regular treatment over long periods.

Public health relevance (burden of disease)

Globally, 20 million people, or about 0.9% of the world's population, are estimated to have schizophrenia (*2*). As estimated by the Global Burden of Disease (GBD) study 2017, schizophrenia contributes 12.66 million disability-adjusted life years (DALYs) to the global burden of disease (*3*).

More than 50% of individuals who receive a diagnosis of schizophrenia have intermittent but long-term psychiatric problems, and about 20% have chronic symptoms and disability (*4*). Regular pharmacological treatment from the early stages of the disease may be key to preserving neurocognitive abilities, preventing structural brain changes, and delaying progression to chronic functional deterioration, resulting in better quality of life and increased survival (*5*). Life expectancy in people with schizophrenia is about 14 years shorter than the general population (*6*).

Adherence to treatment is an important issue with only one in three people with schizophrenia fully adhering to antipsychotic treatment (*7*, *8*). Together with other factors, non-adherence to medication is a predictor of relapse (*9*). Long-acting injectable antipsychotic medicines were developed with the primary aim of reducing non-adherence.

Median treatment coverage for schizophrenia in low- and middle-income countries is estimated to be about 30%. Almost two thirds of people with schizophrenia and related disorders in low- and middle-income countries do not receive adequate treatment. The treatment gap for schizophrenic disorders was larger in lower-income countries (89%) than in lower-middle-income (69%) and upper-middle-income countries (63%). The size of the treatment gap shows a significant negative association with: the prevalence of schizophrenic disorders in the general population; gross national income; the availability of psychiatric

hospital beds; the number of psychiatrists per 100 000 population; and the number of nurses in mental health facilities per 100 000 population (*10*).

Summary of evidence: benefits (from the application)

The application presented the results of a systematic review and network meta-analysis of 78 randomized controlled trials (11 505 participants) evaluating the comparative efficacy, acceptability and tolerability of long-acting antipsychotic medicines in adults with chronic non-affective psychosis (*11*). The primary outcomes were relapse rate and all-cause discontinuation of the medication (the latter as a measure of "acceptability"). Secondary outcomes included: efficacy measured as mean change in scores on validated rating scales measuring psychopathology and quality of life; functioning; and hospitalizations.

Relapse rate

Sixty-nine studies (11 176 participants) contributed data for this outcome. Various long-acting antipsychotic injections were significantly more effective than placebo in preventing relapse, including: paliperidone 3-month (risk ratio (RR) 0.27, 95% confidence interval (CI) 0.17 to 0.42), fluphenazine (RR 0.34, 95% CI 0.24 to 0.48), risperidone (RR 0.34, 95% CI 0.23 to 0.52) and paliperidone 1-month (RR 0.39; 95% CI 0.30 to 0.50).

Head-to-head comparisons showed paliperidone 3-month, aripiprazole and fluphenazine were more effective than haloperidol. Results of the network meta-analysis were consistent with results from pairwise meta-analyses, with the exception of haloperidol versus placebo (favouring placebo in the direct estimate) and fluphenazine versus haloperidol (not significant in the direct estimate).

Paliperidone 3-month ranked best based on the mean surface under the cumulative ranking curve. Compared to placebo, the certainty of evidence was rated as high for paliperidone 3-month and paliperidone 1-month, and moderate for risperidone.

Acceptability (all-cause discontinuation)

Seventy-four studies (11 385 participants) contributed data for this outcome. Most long-acting antipsychotic injections were significantly more acceptable than placebo, including paliperidone 3-month (RR 0.60, 95% CI 0.43 to 0.84), haloperidol (RR 0.64, 95% CI 0.50 to 0.81), fluphenazine (RR 0.67, 95% CI 0.55 to 0.81), risperidone (RR 0.70, 95% CI 0.57 to 0.85) and paliperidone 1-month (RR 0.70, 95% CI 0.58 to 0.85).

Head-to-head comparisons showed aripiprazole to be significantly superior to fluphenazine, paliperidone 1-month and risperidone, among others. Results of the network meta-analyses were consistent with those from pairwise meta-analyses, with some exceptions, including aripiprazole versus paliperidone 1-month (not significant in the direct estimate).

Zuclopenthixol, clopenthixol, aripiprazole and paliperidone 3-month ranked best based on the mean surface under the cumulative ranking curve. Compared with placebo, the certainty of evidence was rated as high for paliperidone 3-month, and moderate for fluphenazine and paliperidone 1-month. For most of the head-to-head comparisons, the certainty of evidence was rated low or very low due to within-study bias and imprecision.

Efficacy measured as mean change in scores on validated rating scales

Risperidone (standardized mean difference (SMD) 0.82, 95% CI 0.34 to 1.30) and paliperidone 1-month (SMD 0.49, 95% CI 0.12 to 0.86) were among the second-generation antipsychotic medicines found to be significantly better than placebo for this outcome. No significant differences were observed in the head-to-head comparisons.

Quality of life

Data were available only for aripiprazole, risperidone and paliperidone 1-month for this outcome (placebo was not included). In head-to-head comparisons, aripiprazole was superior to paliperidone 1-month.

Hospitalization

Compared with placebo, treatment with aripiprazole, paliperidone 3-month, haloperidol, fluphenazine and paliperidone 1-month resulted in significantly lower hospitalization rates.

Functioning

In pairwise meta-analyses, no significant differences between treatments were seen for patient functioning, except for paliperidone 3-month which resulted in better patient functioning than placebo based on results of one study. A network meta-analysis could not be carried out.

With respect to the formulations proposed for listing (paliperidone 1-month and risperidone) head-to-head comparisons in the network meta-analysis showed that these medicines are:

- superior to placebo in reducing the risk of relapse, with effect sizes similar to those of other long-acting antipsychotic medicines included in the analysis, and high (paliperidone 1-month) and moderate (risperidone) certainty of evidence. No statistically significant differences emerged when compared head-to-head with other long-acting antipsychotic medicines.
- more acceptable than placebo in terms of overall dropouts (a pragmatic measure of the balance between efficacy and tolerability), with effect sizes similar to those of other long-acting antipsychotic

medicines included in the analysis, and moderate (paliperidone 1-month) and low (risperidone) evidence. No statistically significant differences emerged when compared head-to-head with other long-acting antipsychotic medicines, except for aripiprazole, which showed a better acceptability profile compared with both paliperidone 1-month and risperidone.

According to a large Swedish database study (*12*), in which 29 823 adults with a diagnosis of schizophrenia were followed between 2006 and 2013, both paliperidone 1-month and risperidone appeared effective in preventing psychiatric rehospitalization compared with no use of antipsychotic medicines (paliperidone: hazard ratio (HR) 0.51, 95% CI 0.41 to 0.64; risperidone: HR 0.61, 95% CI 0.55 to 0.68), and compared with oral olanzapine (paliperidone: HR 0.72, 95% CI 0.62 to 0.83; risperidone: HR 0.80, 95% CI 0.73 to 0.87). The effect size was comparable to those of other long-acting antipsychotic medicines.

Although comparability of oral and long-acting antipsychotic medicines is debated, two systematic reviews and meta-analyses of randomized trials failed to detect significant differences between these two formulations in terms of efficacy, overall acceptability, tolerability and common adverse events (*13*, *14*).

Summary of evidence: harms (from the application)

The systematic review and network meta-analysis presented in the application considered dropouts as a result of adverse events (as a measure of "tolerability"), weight gain, hyperprolactinaemia, extrapyramidal symptoms and QTc prolongation, and sedation (*11*).

Dropouts due to adverse events

Paliperidone 1-month was less tolerable than placebo (RR 1.87, 95% CI 1.02 to 3.40), while for other long-acting antipsychotic medicines, no significant differences were observed compared with placebo.

Weight gain

Significantly higher weight gain occurred with aripiprazole, paliperidone 1-month and paliperidone 3-month, compared with placebo.

Hyperprolactinaemia

The risk of hyperprolactinaemia was significantly higher for olanzapine, paliperidone 1-month and paliperidone 3-month compared with placebo.

Extrapyramidal symptoms

No long-acting antipsychotic medicine showed a significantly higher risk of extrapyramidal symptoms compared with placebo.

QTc prolongation and sedation

In pairwise meta-analyses, no significant differences between treatments emerged, except for paliperidone 3-month which showed a lower risk of QTc prolongation than paliperidone-LAI 1-month, based on the results of one study.

Previous systematic reviews and meta-analyses found no relevant differences between the oral and long-acting injection formulations of the same antipsychotic medication (*13*, *14*). A network meta-analysis (*15*) showed that both oral risperidone and paliperidone were worse than placebo in terms of:

- weight gain: paliperidone (mean difference (MD) 1.49 kg, 95% CI 0.98 to 2.00 kg; 1536 participants; high-certainty evidence) and risperidone (MD 1.44 kg, 95% CI 1.05 to 1.83 kg; 2521 participants; high-certainty evidence);
- use of antiparkinson medications: paliperidone (RR 1.61, 95% CI 1.17 to 2.10; 1355 participants; very low-certainty evidence) and risperidone (RR 1.80, 95% CI 1.40 to 2.38; 2174 participants; low-certainty evidence);
- prolactin increase: paliperidone (MD 48.51 ng/mL, 95% CI 43.52 to 53.51 ng/mL; 1067 participants; moderate-certainty evidence) and risperidone (MD 37.98 ng/mL, 95% CI 34.64 to 41.38 ng/mL; 1761 participants; moderate-certainty evidence).

Another systematic review and meta-analysis assessed the risk of death associated with long-acting injectable and oral antipsychotic medicines in people with schizophrenia (*16*). Up to 52 randomized controlled trials were included (17 416 participants). Neither pooled nor individual long-acting injectable antipsychotic medicines (aripiprazole, fluphenazine, olanzapine, paliperidone and risperidone) differed from placebo regarding the incidence of all-cause death (overall RR 0.64, 95% CI 0.24 to 1.70; 18 studies; 5919 participants). Similarly, pooled long-acting injectable antipsychotic medicines (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone and zuclopenthixol) did not differ from pooled oral antipsychotic medicines with regard to all-cause death (overall RR 0.71, 95% CI 0.38 to 1.34; 24 studies; 7879 participants). Secondary analyses showed no differences between long-acting injectable antipsychotic medicines and both placebo and oral antipsychotic medicines in terms of suicide. The risk of death was similar for individual long-acting injectable antipsychotic medicines and oral antipsychotic medicines.

Additional evidence (not in the application)

Not applicable

WHO guidelines

According to WHO guidelines, people with psychotic disorders (including schizophrenia), who require long-term antipsychotic treatment, can be offered depot antipsychotic medicines instead of oral medications as part of a treatment plan. The guidelines also recommend that patients and carers should be offered clear and accessible information in a suitable format about the use and possible side-effects of oral versus depot preparations (*17*, *18*).

Costs/cost–effectiveness

Costs and worldwide availability of long-acting injectable antipsychotic medicines vary. Although currently both risperidone and paliperidone 1-month long-acting injections are marketed by the innovator company Janssen, most of the patents that prevent the marketing of generics have already expired, and most of the remaining will expire soon.

A 1-year mirror-image study conducted in the United Kingdom, including 30 people receiving aripiprazole long-acting injection and 84 receiving paliperidone 1-month long-acting injection, showed a significant reduction in both bed occupancy and hospital admission compared with the period before the introduction of the treatment. Estimated minimum savings were £ 14 175 for aripiprazole and £ 13 750 for paliperidone (*19*). Similarly, a mirror-image study conducted in Spain, including 71 outpatients starting paliperidone 1-month long-acting injection, showed that fewer hospitalizations, shorter hospitalization days, fewer emergency assists and a decrease in the mean number of antipsychotic medicines used per patient were associated with the long-acting treatment. These reductions led to an overall reduction in inpatient spending (savings of € 175 766) and a 32% increase in spending on antipsychotic medicines (equivalent to € 151 127) after 1 year of treatment (*20*).

The cost–effectiveness of paliperidone versus haloperidol decanoate in the maintenance treatment of schizophrenia was evaluated in the ACLAIMS trial (*21*). This trial included 311 participants allocated to haloperidol decanoate and paliperidone. Paliperidone had a better efficacy profile in terms of quality-adjusted life years (QALY) but also greater average quarterly inpatient, outpatient and medications costs. The incremental cost–effectiveness ratio for paliperidone was US$ 508 241 per QALY. Overall, haloperidol decanoate was more cost-effective than paliperidone palmitate, and the markedly higher on-patent costs of paliperidone were not justified by its slightly greater benefits (*21*).

Table 9 compares costs of long-acting injection formulations of various antipsychotic medicines in different countries.

Table 9
Costs (in US$) of long-acting injection formulations of antipsychotic medicines, by country

Medicine	Italy	United Kingdom	United States of America	Brazil	India	South Africa
Risperidone						
25 mg	185	105	540	–	–	121
37.5 mg	240	146	805	222	–	164
50 mg	300	188	1071	320	121	207
Paliperidone 1-month						
50 mg	398	242	985	–	–	193
75 mg	514	323	1474	–	121	281
100 mg	655	414	1962	326	121	370
150 mg	804	517	2938	–	121	547
Paliperidone 3-month						
175 mg	1197	728	2938	–	–	–
263 mg	1545	969	4402	–	–	–
350 mg	1930	1242	5867	–	–	–
525 mg	3105	1553	8796	–	–	–
Fluphenazine						
25 mg	5.30	30	75	34	0.68	19
100 mg	–	58	–	–	–	–
Haloperidol						
50 mg	11.30	25.00	33.00	3.60	0.08	–
100 mg	–	33.00	40.00	–	–	–

Availability

Risperidone long-acting injection has been approved by the US Food and Drug Administration for the treatment of schizophrenia, and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder. Risperidone long-acting injection has also been approved by the European Medicines Agency for the maintenance treatment of schizophrenia in people currently stabilized with oral antipsychotic medicines.

Paliperidone long-acting injection 1-month has been approved by the US Food and Drug Administration: for treatment of schizophrenia; for treatment of schizoaffective disorder as monotherapy; and as an adjunct to mood stabilizers or antidepressants. It is also approved by the European Medicines Agency for the maintenance treatment of schizophrenia in adults whose disease has already been stabilized on treatment with paliperidone or risperidone.

Paliperidone long-acting injection 3-month has been approved by the US Food and Drug Administration for the treatment of schizophrenia in patients after they have been adequately treated with paliperidone long-acting injection 1-month for at least 4 months, and by the European Medicines Agency for maintenance treatment of schizophrenia in adult patients who are clinically stable on paliperidone long-acting injection 1-month.

According to the manufacturer Janssen, paliperidone long-acting injection 1-month and 3-month are currently approved in 103 and 91 countries, respectively, including the USA, countries of the European Union, Japan, Ghana and South Africa. Risperidone long-acting injection is currently licensed in 59 countries. The 12.5 mg dose is used as the titration/starting dose only and is currently only available in Canada and the USA.

Other considerations

Although paliperidone palmitate 3-month long-acting injection was shown to be effective and acceptable, the applicants decided not to consider this medication for the present proposal for the following reasons.

- It has been available only in relatively recent times (approved by the European Medicines Agency in 2016), it not yet commonly used in clinical practice and worldwide its availability may be limited.
- Some concerns had been raised about the randomized study comparing paliperidone palmitate 3-month and placebo (*22*). Study participants underwent a stabilization phase with paliperidone 1-month before randomization which might have inflated the effect size in favour of paliperidone.
- More research is needed to rule out possible unintended consequences of this formulation of paliperidone, including the effects of reduced doctors' visits due to the longer dosing interval. In addition, the cumulative monthly dose of paliperidone 3-month is slightly higher than that of paliperidone 1-month and this may affect toxicity and tolerability (*23*).

In general, injectable long-acting antipsychotic medicines are administered by health care professionals and require some technical precautions. Paliperidone is supplied in prefilled syringes and can be stored at room temperature, risperidone

requires reconstitution and cold chain storage. If cold chain storage is not available, it can be stored at room temperature so long as the temperature does not exceed 25 °C (77 °F), and it is used within 7 days. In some low- and middle-income countries and in humanitarian emergency settings, these logistical constraints and the need for trained health care workers may prevent the use of long-acting risperidone.

Committee recommendations

The Expert Committee considered that long-acting injectable antipsychotic medicines are a valuable treatment option to increase adherence to treatment and reduce relapse in adults with schizophrenia and related psychotic disorders. The Committee also noted with concern the uncertainty of current and future availability of fluphenazine injection, which is the only long-acting injectable antipsychotic medicine included on the EML at the moment, and considered that the availability of alternative medicines would be important to meet the public health need for such treatments. The Committee noted that long-acting injectable antipsychotic medicines are an established treatment option for schizophrenia and are recommended in existing WHO (mhGAP) guidelines. In particular, the Committee acknowledged that long-acting injectable antipsychotic medicines are useful in low-resource settings, where many factors might impede regular monitoring and follow-up of patients.

The Committee noted that the available data suggest benefits of long-acting injectable antipsychotic medicines versus oral antipsychotic medicines in preventing hospitalization or relapse, especially in populations with low treatment adherence. The effectiveness and overall safety of first-generation and second-generation antipsychotic medicines are similar. The availability of agents with different side-effect profiles may support the selection of one treatment over another given a patient's clinical status and vulnerabilities.

The Expert Committee therefore recommended the addition of paliperidone palmitate 1-month long-acting injection to the core list of the EML for maintenance treatment of schizophrenia in adults stabilized on oral therapy. The listing is recommended with a square box specifying risperidone long-acting injection as a therapeutic alternative.

The Committee also noted and welcomed the planned comprehensive review by the WHO Department of Mental Health and Substance Use of the mental health sections of the EML and EMLc to achieve optimal alignment between the Model Lists and recommendations of the WHO mental health treatment guidelines.

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24.5 Medicines for disorders due to psychoactive substance use

Bupropion – addition – EML

Bupropion hydrochloride **ATC Code: N06AX12**

Proposal

Addition of bupropion hydrochloride to the core list of the EML as an aid to smoking cessation in adults.

Applicant

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WHO technical department

Department of Health Promotion, No Tobacco Unit

EML/EMLc

EML

Section

24.5 Medicines for disorders due to psychoactive substance use

Dose form(s) & strengths(s)

Tablet, sustained-release: 150 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Bupropion hydrochloride has not been evaluated before for inclusion on the EML.

Nicotine replacement therapy (NRT), as chewing gum or transdermal patch formulations, has been included on the EML since 2009. The Expert Committee recommended listing on the basis of the public health need, high-quality evidence of effectiveness, and acceptable safety and cost–effectiveness. Other formulations were not recommended for inclusion at the time because less evidence was available of comparative safety, effectiveness and cost in different populations (*1*).

Public health relevance (burden of disease)

Tobacco smoking is still the leading cause of premature disability and death around the world (*2*). Cigarette smoke contains an estimated 7000 different chemical compounds of which at least 70 are proven or suspected human carcinogens, including: arsenic, benzene, formaldehyde, lead, nitrosamines and polonium 210. Tobacco smoke also contains poisonous gases: ammonia, butane, carbon monoxide (CO), hydrogen cyanide and toluene. More than half of all long-term smokers die from a disease caused by tobacco use, with an average loss of at least 10 years of life (*3*). Smoking causes 87% of lung cancer deaths, 61% of pulmonary disease deaths (chronic obstructive pulmonary disease (COPD) and emphysema) and one in three cancer deaths. For every person who dies from smoking, at least 30 people live with serious smoking-related illnesses (*3*).

According to WHO (*4*):

- The tobacco epidemic is one of the biggest public health threats the world has ever faced.
- Globally, 1.3 million people use tobacco, of whom 80% live in low- and middle-income countries.
- Tobacco use contributes to poverty by diverting household spending away from basic needs.
- Over 8 million people a year die from tobacco use.
- The economic costs of tobacco use are substantial.

Estimates from 2012 are that the total global economic cost of smoking was US$ 1436 billion, equivalent to 1.8% of the world's annual gross domestic product (GDP), with about 40% of the total economic cost borne by developing countries (*5*).

The scale of human and economic harms that the tobacco industry imposes is large and preventable. In response, in 2003, WHO Member States unanimously adopted the WHO Framework Convention on Tobacco Control (WHO FCTC), which is currently endorsed by 182 Parties and covers more than 90% of the world's population. To scale up implementation of the main demand-reduction (i.e. tobacco control) provisions of the WHO FCTC, the WHO introduced MPOWER in 2007, with "O" related to offering treatment. The six MPOWER measures are:

- **M**onitor tobacco use and prevention policies
- **P**rotect people from tobacco use
- **O**ffer help to quit tobacco use
- **W**arn about the dangers of tobacco
- **E**nforce bans on tobacco advertising, promotion and sponsorship
- **R**aise taxes on tobacco.

Quitting smoking brings health benefits and when smokers become aware of the dangers of tobacco use, most want to quit. Yet, without medications or cessation support, only about 4% of attempts to stop using tobacco will succeed. Professional support and proven cessation medications can more than double a tobacco user's chance of successfully quitting (*5*).

As stated in the 2019 WHO report on the global tobacco epidemic (*6*), "Every country has an obligation to protect the health of its people, and all parties to the WHO FCTC have made a specific commitment to implement strong tobacco control policies, including effective cessation services, as an important means of fulfilling their obligation to protect the health of their people."

Tobacco dependence is characterized as a physiological dependence (addiction to nicotine) and a behavioural (or conditioned) habit of using tobacco. Hence, for maximal effectiveness, as recommended by clinical practice guidelines, tobacco dependence treatment engages a multipronged approach (*7*–*9*). Addiction can be treated with evidence-based medications for smoking cessation, and the behavioural habit can be treated through counselling and behaviour change programmes. Either cessation medication or counselling alone has evidence of effectiveness, but the best outcomes are with a combination of both approaches. The availability of interventions and their use are likely to vary. Having many cessation medication options available for clinicians and smokers for tobacco treatment is essential for tackling the significant global harms of tobacco use.

Summary of evidence: benefits (from the application)

The efficacy of bupropion sustained release (SR) as an aid to smoking cessation has been demonstrated in many placebo-controlled, double-blind trials.

The application describes three trials conducted by the manufacturer (GlaxoSmithKline, GSK) in non-depressed chronic cigarette smokers (n = 1940, smoking > 15 cigarettes a day) (*10*). In these trials, bupropion SR was used in conjunction with individual smoking cessation counselling. Treatment with bupropion SR was started at 150 mg a day while the participant was still smoking and then increased after 3 days to 150 mg twice daily. Abstinence rates were determined by participant daily diaries and verified by CO levels in expired air and are the proportions of all participants initially enrolled (i.e. intent-to-treat analysis) who abstained in the specified week.

The first trial (n = 615), conducted at three clinical centres, evaluated dose–response (*11*). Participants were treated for 7 weeks with one of three doses of bupropion SR (100, 150 or 300 mg a day) or placebo. Participants set a target quit date after 1 week of medication (usually day 8). Table 10 shows CO-confirmed weekly point prevalence quit rates at week 6 (final week of study medication) and at months 3, 6 and 12. Treatment with bupropion SR (100,

150 or 300 mg a day) was more effective than placebo in helping participants achieve abstinence at week 6 and month 3. Treatment with bupropion at 150 mg or 300 mg a day was more effective than placebo in helping participants achieve abstinence at months 6 and 12. Rates of continuous abstinence from the target quit date to the end of treatment were 10.5% in the placebo group, 13.7% in the 100 mg group, 18.3% in the 150 mg group and 24.4% in the 300 mg group. The rate of continuous abstinence was significantly better in the bupropion 300 mg group than in the placebo group ($P < 0.001$) and the group that received 100 mg of bupropion ($P < 0.02$).

Table 10
Dose–response trial: carbon monoxide-confirmed weekly point prevalence quit rates

Treatment groups (7-week)	Quit rate (%)			
	Week 6[a]	Month 3	Month 6	Month 12
Bupropion SR 300 mg/day ($n = 156$)	44.2**	29.5**	26.9*	23.1*
Bupropion SR 150 mg/day ($n = 153$)	38.6**	26.1*	27.5*	22.9*
Bupropion SR 100 mg/day ($n = 153$)	28.8*	24.2*	24.2	19.6
Placebo ($n = 153$)	19.0	14.4	15.7	12.4

SR: sustained release.
[a] Final week of study medication.
*$P < 0.05$; **$P < 0.001$ relative to placebo.
Hurt RD, et al., 1997 (*11*).

The second trial was a comparator combination treatment trial ($n = 893$) conducted at four clinics, which evaluated 9-week treatments of: bupropion SR 300 mg a day, nicotine patch 21 mg a day, a combination of bupropion SR 300 mg and nicotine patch 21 mg a day, and placebo (*12*). Nicotine patch 21 mg a day was added to treatment with bupropion SR after about 1 week when the participant reached the target quit date. During weeks 8 and 9 of the trial, the patch was tapered to 14 and 7 mg a day, respectively. The primary outcome was CO-verified point-prevalence abstinence at 6 and 12 months follow-up. Bupropion SR and the combination of bupropion SR and nicotine patch were better than placebo in helping participants to achieve and maintain abstinence from smoking (Table 11). The treatment combination of bupropion SR and nicotine patch showed the highest rates of continuous abstinence throughout the trial; however, the quit rates for the combination were not significantly higher than for bupropion SR alone ($P > 0.05$).

Table 11
Comparator clinical trial: carbon monoxide-confirmed point prevalence quit rates

Treatment groups (9-week)	Quit rate (%) [a]	
	6 months	12 months
Bupropion SR 300 mg plus nicotine patch 21 mg (*n* = 245)	38.8	35.5
Bupropion SR 300 mg (*n* = 244)	34.8	30.3
Nicotine patch 21 mg (*n* = 244)	21.3	16.4
Placebo (*n* = 151)	18.8	15.6

SR: sustained release.

[a] Bupropion SR plus nicotine patch and bupropion SR alone compared with placebo at 6 and 12 months, $P \leq 0.001$; nicotine patch compared with placebo at 6 and 12 months, $P = 0.53$ and $P = 0.84$, respectively; bupropion SR plus nicotine patch compared with bupropion SR alone at 6 and 12 months, $P = 0.37$ and $P = 0.22$, respectively.

Jorenby DE, et al., 1999 (*12*).

The third trial, at five clinics, examined long-term maintenance treatment with bupropion SR (*13*). Participants (n = 784) received open-label bupropion SR 300 mg a day for 7 weeks. After 7 weeks, 429 participants who quit smoking while receiving bupropion SR were then randomized to receive bupropion SR 300 mg a day or placebo for a total trial duration of 1 year. Abstinence from smoking was determined by self-report and verified by expired air CO levels. Smoking point prevalence abstinence was significantly higher in the bupropion SR group than in the placebo group at the end of drug therapy at week 52 (55% versus 42%, respectively; $P = 0.008$) and at week 78 (48% versus 38%, respectively; $P = 0.034$) but did not differ at the final follow-up visit at week 104 (42% versus 40%, respectively; $P > 0.05$). The median time to relapse was significantly greater for bupropion SR recipients than for placebo recipients (156 days versus 65 days; $P = 0.021$). The continuous abstinence rate was higher in the bupropion SR group than in the placebo group at study week 24 (17 weeks after randomization) (52% versus 42%; $P = 0.037$), but did not differ between groups after week 24.

Another 6-month trial of long-term maintenance treatment with bupropion SR reported hazard ratios (HR) for relapse that statistically significantly favoured bupropion SR over placebo at 6 months, the end of treatment (HR 0.59, 95% CI 0.37 to 0.92) and at 12 months, the 6-month follow-up (HR 0.66, 95% CI 0.42 to 0.96) (*14*). However, the advantage of bupropion SR was lost on stopping the drug.

Quit rates in clinical trials are influenced by the population selected. Quit rates in an unselected population may be lower than the above rates. Quit rates for bupropion SR were similar in participants with and without prior attempts to quit using NRT.

Across trials, during active treatment, withdrawal symptoms were significantly reduced in participants randomized to treatment with bupropion SR compared with placebo. Reductions in the following withdrawal symptoms were most pronounced: irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending on the trial and the measure used, treatment with bupropion SR showed evidence of reduction in craving for cigarettes or urge to smoke compared with placebo.

Pfizer conducted two identically designed double-blind preauthorization comparative clinical trials of varenicline versus bupropion SR for smoking cessation – studies A3051036 and A2051028 (*15*, *16*). The treatment arms were varenicline (1 mg twice daily), bupropion SR (150 mg twice daily) and placebo. In these 52-week duration studies, participants received treatment for 12 weeks, followed by a 40-week non-treatment phase. In addition to an educational booklet on smoking cessation, participants received up to 10 minutes of smoking cessation counselling at each weekly treatment visit. Participants can smoke in the first week of medication dosing and set a date for stopping smoking. The primary endpoint of the two studies was 4-week continuous abstinence from smoking during weeks 9–12 confirmed by exhaled CO. After the 40-week non-treatment phase, a key secondary endpoint for both studies was the continuous abstinence during weeks 9–52. The continuous abstinence rates during weeks 9–12 and 9–52 from these studies are shown in Table 12. Compared with placebo, bupropion SR had significantly higher continuous abstinence rates at weeks 9–12 in both trials and at weeks 9–52 in one of the trials. Varenicline was superior to bupropion SR at weeks 9–12 in both trials and at weeks 9–52 in one of the trials.

Table 12
Varenicline compared with bupropion SR for smoking cessation in the Pfizer comparative clinical trials

Treatment groups	Study A3051028 (*16*) (*n* = 1025)		Study A3051036 (*15*) (*n* = 1027)	
	Weeks 9–12	Weeks 9–52	Weeks 9–12	Weeks 9–52
	Continuous abstinence rate (%)			
Varenicline 2 mg/day	44.0	21.9	43.9	23.0
Bupropion SR 300 mg/day	29.5	16.1	29.8	14.6
Placebo	17.7	8.4	17.6	10.3

Table *continued*

Treatment groups	Study A3051028 (*16*) (*n* = 1025)		Study A3051036 (*15*) (*n* = 1027)	
	Weeks 9–12	Weeks 9–52	Weeks 9–12	Weeks 9–52
	Odds ratio for continuous abstinence			
Varenicline vs placebo	3.85***	3.09***	3.85***	2.66***
Bupropion vs placebo	2.00***	2.09**	1.99***	1.50
Varenicline vs bupropion	1.93***	1.46	1.90***	1.77**

vs: versus.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Across both studies during active treatment, participant-reported outcome measures showed that craving and withdrawal (urge, negative effect and insomnia) were significantly lower in participants randomized to receive bupropion SR versus placebo. Bupropion SR also significantly reduced positive reinforcing effects of smoking during treatment compared with placebo.

A Cochrane meta-analysis was conducted to assess the evidence for the efficacy, safety and tolerability of medications with antidepressant properties, including bupropion SR, in assisting long-term smoking cessation in people who smoke cigarettes (*17*). The literature search was last updated in May 2019 and was restricted to randomized controlled trials with smoking cessation treatment outcomes reported at 6 months or longer. The meta-analysis included samples of any age; studies on smoking treatment in pregnancy were excluded. When multiple doses of bupropion were compared in a trial, data from the 300 mg/day arm were used. The efficacy findings are summarized in the following list.

- High-certainty evidence confirmed the benefit of bupropion SR compared with placebo as a single pharmacotherapy for smoking cessation (risk ratio (RR) 1.64, 95% CI 1.52 to 1.77; $I^2 = 15\%$; 45 studies, 17 866 participants).
- Treatment effects of bupropion SR for quitting smoking were comparable across settings and types of behavioural support studied (group versus individual, low-intensity, i.e. routine care).
- Treatment effects of bupropion SR for quitting smoking were comparable for participants with psychiatric conditions (RR 1.67, 95% CI 1.3 to 2.15; $I^2 = 0\%$; five studies, 2180 participants) and

without a history of psychiatric conditions (RR 1.67, 95% CI 1.3 to 2.15; I^2 = 23%; 42 studies, 15 686 participants). Trials comparing bupropion SR to placebo found no evidence of an interaction between depression and bupropion SR treatment effects. The samples were recruited as motivated to quit, and those with psychiatric conditions were stable on treatment.

- Adding bupropion SR to NRT (RR 1.19, 95% CI 0.94 to 1.51; I^2 = 52%; 12 studies, 3487 participants) or varenicline (RR 1.21, 95% CI 0.95 to 1.55; I2 = 15%; three studies, 1057 participants) did not appear to provide additional benefit compared with treatment with NRT or varenicline alone, respectively.
- The evidence does not suggest a difference in the efficacy of bupropion SR and NRT (RR 0.99, 95% CI 0.91 to 1.09; I^2 = 18%; 10 studies, 8230 participants), or bupropion SR and nortriptyline (RR 1.30 (favouring bupropion SR), 95% CI 0.93 to 1.82; I^2 = 0%; three studies, 417 participants) for smoking cessation.
- Bupropion SR had lower smoking cessation rates compared with varenicline (RR 0.71, 95% CI 0.64 to 0.79; I^2 = 0%; six studies, 6286 participants).

Smokers with COPD

In a randomized, double-blind trial conducted by GSK, bupropion SR was evaluated in 404 participants with mild to moderate COPD defined as postbronchodilator forced expiratory volume 1/forced vital capacity (FEV1/FVC) < 70% and FEV1 per cent predicted normal value ≥ 50%, and a diagnosis of chronic bronchitis, emphysema and/or small airways disease (*18*). Participants aged 36 to 76 years were randomized to bupropion SR 300 mg a day (n = 204) or placebo (n = 200) and treated for 12 weeks. All participants were chronic smokers with a smoking history of about 51 pack years. Treatment with bupropion SR was started at 150 mg a day for 3 days while the participant was still smoking and increased to 150 mg twice daily for the remaining treatment period. Abstinence from smoking was determined by participant daily diaries and verified by CO levels in expired air. Quitters were defined as participants who were abstinent during the last 4 weeks of treatment. Participants treated with bupropion SR had higher abstinence rates than those who received the placebo in the last 4 weeks of treatment (22% versus 12%, P = 0.011). Continuous abstinence rates from weeks 4–12 and weeks 4–26 were also significantly higher in participants receiving bupropion SR than in those taking the placebo (18% versus 10% (P = 0.021) and 16% versus 9%, (P = 0.040)). Furthermore, symptoms of tobacco craving and withdrawal were reduced in those receiving bupropion SR.

Smokers with cardiovascular disease

Several randomized controlled trials and meta-analyses have examined use of bupropion SR for treating smoking in adults with cardiovascular disease (CVD).

A randomized, double-blind, multicentre trial funded by GSK investigated the safety and efficacy of bupropion SR in promoting abstinence from smoking in 629 participants with CVD who smoked > 10 cigarettes a day (*15*). Participants received bupropion SR (150 mg twice daily) or placebo for 7 weeks with brief motivational support, with a follow-up assessment at 52 weeks. The primary efficacy endpoint was continuous abstinence from smoking from week 4 to week 7. Secondary endpoints were continuous abstinence at weeks 4–12, 4–26 and 4–52. Continuous smoking abstinence rates from weeks 4–7 were significantly higher in participants receiving bupropion SR compared with placebo (43% versus 19%, OR 3.27, 95% CI 2.24 to 4.84). Continuous abstinence rates from weeks 4–26 and 4–52 continued to be more than double for bupropion SR compared with placebo (27% versus 11% and 22% versus 9%, both $P < 0.001$). In both groups, no clinically significant changes in blood pressure and heart rate were seen throughout the treatment phase. After 7 weeks of bupropion SR treatment, more than twice as many smokers with CVD had quit smoking at 1 year compared with those receiving placebo.

A randomized controlled trial evaluated the safety and efficacy of bupropion SR in 247 hospitalized smokers with acute CVD (*19*). Participants were treated for 12 weeks with bupropion SR 300 mg or placebo. Counselling was provided to all participants in the hospital and for 12 weeks following discharge. Cotinine-confirmed abstinence outcomes were reported at 3 months (end-of-treatment) and 12 months. Validated tobacco abstinence rates in the bupropion SR and placebo groups were 37% versus 27% (OR 1.61, 95% CI 0.94 to 2.76) at 3 months and 25% versus 21% (OR 1.23, 95% CI 0.68 to 2.23) at 12 months. The adjusted OR, after controlling for cigarettes smoked a day, depression symptoms, prior bupropion SR use, hypertension and length of stay, was 1.91 (95% CI 1.06 to 3.40) at 3 months and 1.51 (95% CI 0.81 to 2.83) at 12 months. Bupropion SR and placebo groups did not differ in cardiovascular mortality at 12 months (0% versus 2%), in blood pressure at follow-up or in cardiovascular events at end-of-treatment (16% versus 14%, incidence rate ratio (IRR) 1.22 (95% CI 0.64 to 2.33) or at 12 months (26% versus 18%, IRR 1.56, 95% CI 0.91 to 2.69). The investigators concluded that bupropion SR improved short-term but not long-term smoking cessation rates compared with intensive counselling and appeared to be safe in hospitalized smokers with acute CVD.

A meta-analysis of three randomized controlled trials (773 participants) was conducted to determine the efficacy and safety of bupropion SR therapy started in hospital for smoking cessation in patients with CVD (*20*). Participants were predominantly men (range of means 69–84%) and hospitalized with acute

coronary syndrome (range of means 66–100%). Treatment duration ranged from 8 to 12 weeks. At the end of treatment, bupropion SR was associated with a significant increase in point prevalence abstinence (RR 1.21, 95% CI 1.02 to 1.45) but not continuous abstinence (RR 1.19, 95% CI 0.97 to 1.45). At 12 months, bupropion SR was not associated with a significant increase in point prevalence abstinence (RR 1.17, 95% CI 0.92 to 1.48) or continuous abstinence (RR 1.16, 95% CI 0.90 to 1.50). Pooled analysis results for major adverse cardiac and cerebrovascular events were inconclusive (RR 1.28, 95% CI 0.93 to 1.78). Bupropion SR improved abstinence over placebo at the end of treatment but not at 12 months.

A network meta-analysis was conducted to evaluate the efficacy and safety of pharmacological smoking cessation interventions in CVD patients in randomized controlled trials (*21*). Smoking abstinence at 6 and 12 months was examined using the most rigorous criteria reported. Data were pooled across studies for direct comparisons using random-effects models. Network meta-analysis using a graph theoretical approach was used to generate the indirect comparisons. Seven randomized controlled trials (n = 2809) met the inclusion criteria. Varenicline (one trial, RR 2.64, 95% CI 1.34 to 5.21) and bupropion SR (four trials, RR 1.42, 95% CI 1.01 to 2.01) were associated with greater abstinence than placebo, while the evidence for NRTs was inconclusive (two trials, RR 1.22, 95% CI 0.72 to 2.06).

Smokers with current depression

Five trials, all with relatively small sample sizes, reported results of bupropion SR (with or without NRT) versus placebo in smokers with current depression. A meta-analysis of effects across the five trials resulted in a positive, although not significant, effect for the outcome of abstinence at 6 months or longer follow-up (five trials (n = 410); RR 1.37, 95% CI 0.83 to 2.27) (*22*).

Smokers with and without a history of psychiatric disorders

Bupropion SR was evaluated in the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial, a randomized, double-blind, active- and placebo-controlled trial that included participants without a history of psychiatric disorder (non-psychiatric cohort, n = 3912) and participants with a history of psychiatric disorder (psychiatric cohort, n = 4003) (*23*). Participants aged 18 to 75 years, smoking > 10 cigarettes a day were randomized 1:1:1:1 to bupropion SR 150 mg twice daily, varenicline 1 mg twice daily and nicotine patch 21 mg a day with taper or placebo for a treatment period of 12 weeks. Participants were then followed for another 12 weeks post-treatment. The primary focus of the trial was safety in estimating the occurrence of neuropsychiatric adverse events. The main efficacy objectives were measuring continuous abstinence for weeks 9–12 and weeks 9–24 in participants with and

without a psychiatric diagnosis. The primary comparisons were bupropion SR versus placebo and varenicline versus placebo. Nicotine patch was included as an active control.

For the outcome of continuous abstinence rates measured at weeks 9–12 and weeks 9–24, in both cohorts and overall, all active treatments (including bupropion SR) showed significantly greater efficacy in smoking cessation compared with placebo (Table 13 and Table 14). In addition, varenicline showed significantly greater efficacy than bupropion SR and nicotine patch at both weeks 9–12 and 9–24, while no significant differences were found between bupropion SR and nicotine patch in either time period.

Table 13

Treatment comparisons for continuous abstinence from tobacco use in smokers with and without psychiatric disorders, weeks 9–12

Treatment comparisons	Odds ratio (95% CI) for continuous abstinence		
	Group without psychiatric disorders	Group with psychiatric disorders	Total
Bupropion vs placebo	2.26 (1.80, 2.85)	1.87 (1.46, 2.39)	2.07 (1.75, 2.45)
Bupropion vs nicotine patch	0.98 (0.80, 1.20)	0.94 (0.75, 1.16)	0.96 (0.83, 1.11)
Bupropion vs varenicline	0.56 (0.47, 0.68)	0.57 (0.47, 0.71)	0.57 (0.50, 0.65)
Varenicline vs placebo	4.00 (3.20, 5.00)	3.24 (2.56, 4.11)	3.61 (3.07, 4.24)
Varenicline vs nicotine patch	1.74 (1.43, 2.10)	1.62 (1.32, 1.99)	1.68 (1.46, 1.93)
Nicotine patch vs placebo	2.30 (1.83, 2.90)	2.00 (1.56, 2.55)	2.15 (1.82, 2.54)

CI: confidence interval; vs: versus.
Anthenelli RM, et al., 2016 (*23*).

Table 14
Treatment comparisons for smoking cessation in smokers with and without psychiatric disorders, weeks 9–24

Treatment comparisons	Odds ratio (95% CI) for continuous abstinence		
	Group without psychiatric disorders	Group with psychiatric disorders	Overall
Bupropion vs placebo	2.00 (1.54, 2.59)	1.77 (1.33, 2.36)	1.89 (1.56, 2.29)
Bupropion vs nicotine patch	1.02 (0.81, 1.28)	1.07 (0.83, 1.39)	1.04 (0.88, 1.24)
Bupropion vs varenicline	0.67 (0.54, 0.83)	0.71 (0.56, 0.90)	0.69 (0.59, 0.81)
Varenicline vs placebo	2.99 (2.33, 3.83)	2.50 (1.90, 3.29)	2.74 (2.28, 3.30)
Varenicline vs nicotine patch	1.52 (1.23, 1.89)	1.51 (1.19, 1.93)	1.52 (1.29, 1.78)
Nicotine patch vs placebo	1.96 (1.51, 2.54)	1.65 (1.24, 2.20)	1.81 (1.49, 2.19)

CI: confidence interval; vs: versus.
Anthenelli RM, et al., 2016 (*23*).

Healthy adolescent smokers

Four published trials have evaluated bupropion SR for treating smoking in adolescent groups (*24–27*), with one of the trials receiving support from GSK (*25*). Two of the studies were limited to short-term (i.e. 12-week) follow-up (*24*, *27*).

One study evaluated 7-week treatment of bupropion SR at 300 mg or 150 mg a day versus placebo in 312 adolescents aged 14–17 years (*25*). At 6-months follow-up, CO-confirmed 7-day point prevalence abstinence was 8.7% for bupropion SR 300 mg, 1.9% for bupropion SR 150 mg and 5.8% for placebo; RR 1.49 (95% CI 0.55 to 4.02) for bupropion SR 300 mg versus placebo.

The second study examined bupropion SR in combination with nicotine patch versus nicotine patch alone in a sample of 211 adolescents with an average age of 17 years (*26*). In addition to the medications, all participants received weekly 45-minute group sessions with skills training. Compliance with bupropion SR and patch therapy was low and over a third of participants in both groups was lost to follow-up at 6 months. Intention-to-treat cotinine-validated 7-day point prevalence abstinence at 6 months (assuming those lost to follow-up were

still smoking) was 7.8% for bupropion SR plus patch and 7.4% for patch alone (RR 1.05, 95% CI 0.41 to 2.69).

The third study examined bupropion SR versus placebo with or without contingency management in 134 participants between the ages of 12 and 21 years (*24*). CO-confirmed 7-day point prevalence abstinence at 12-week follow-up, combined across contingency management conditions, were 8.2% for bupropion SR versus 3.3% for placebo (calculated pooled effects OR for bupropion SR 2.6, 95% CI 0.5 to 13.6).

The fourth study compared 8 weeks of bupropion SR versus varenicline in 29 adolescents aged 15 to 20 years (*27*). Quit rates, reported as cotinine-confirmed 7-day point prevalence abstinence at 12-week follow-up, were 0% for varenicline versus 7.1% for bupropion SR.

Summary of evidence: harms (from the application)

A systematic review of the clinical effectiveness and cost–effectiveness of bupropion SR and NRT for smoking cessation published in 2002 included a comprehensive assessment of safety and adverse events from participant use of bupropion SR (*28*). The only adverse events reported that were statistically significantly more common with bupropion SR (100 or 300 mg/day) than with placebo were insomnia (34.6% and 42.4% compared with 20.0%) and dry mouth (12.8% and 10.7% compared with 4.5%). This review was limited by the small number of randomized trials at the time (five trials) and the exclusion criteria for participants in those trials.

A 2008 community-based observational cohort study evaluated the safety of bupropion in 11 735 participants (*29*). The most commonly reported adverse events reported were insomnia, nausea and/or vomiting and dizziness.

Adverse effects of bupropion SR are experienced more often than with NRT although the discontinuation rate is similar between the two therapies (*30*). About 9% of participants using either bupropion SR or NRT will discontinue treatment and a further 13% will stop treatment temporarily (*31*). Participants in community-based observational studies report experiencing adverse effects at a higher rate than participants in clinical trials (*32*,*33*); however these community-based studies may include individuals who are unable to distinguish between withdrawal-related symptoms and medication-related symptoms.

The main safety concern with bupropion is the risk of seizures. Seizures have been reported to occur at a rate of about 0.1% in depressed patients treated with up to 300 mg a day (*34*). In a review of 221 clinical papers involving over 4000 participants, no seizures were reported (*35*). In a 2014 Cochrane review of antidepressants for smoking cessation, 10 seizures were reported out of 13 000 participants treated with bupropion (*36*).

The risk of seizure is dose-related and risk can be minimized by gradually increasing the dose and limiting the daily dose to 300 mg. Regardless, bupropion SR is contraindicated in people with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or in those going through abrupt discontinuation of alcohol, benzodiazepines, barbiturates and antiepileptic drugs (*34*).

Pooled data from 10 randomized trials of bupropion SR found the most commonly observed side-effects to be insomnia, headache, dry mouth, rash and/or pruritus, rhinitis and nausea and/or vomiting (*30*).

The EAGLES trial evaluated the neuropsychiatric safety and efficacy of varenicline, bupropion SR and nicotine patch in 8144 smokers with and without psychiatric disorders (*23*). In the bupropion SR arm of the trial, for the primary comparison of bupropion SR versus placebo, the risk difference for neuropsychiatric adverse events was 0.85 (95% CI −0.13 to 2.15), i.e. no statistically significant increased risk of neuropsychiatric adverse events in the composite endpoint with bupropion SR treatment. Following the EAGLES trial results and analysis, the US Food and Drug Administration reported that the risk of mental health side-effects from smoking cessation medications was "lower than previously suspected". New medication labelling was to include updated results of the EAGLES trial but no longer required a risk evaluation and mitigation strategy. The most frequently reported adverse events for each medication in the EAGLES trial are reported in Table 15.

Table 15

Most frequently reported treatment-emergent adverse events (in ≥ 5% of participants in any treatment arm), EAGLES overall safety population

Type of adverse event	No. (%)			
	Varenicline (*n* = 2016)	Bupropion (*n* = 2006)	NRT (*n* = 2022)	Placebo (*n* = 2014)
Total with adverse events	**1503 (74.6)**	**1446 (72.1)**	**1436 (71.0)**	**1345 (66.8)**
Gastrointestinal disorders	*786 (39.0)*	*527 (26.3)*	*481 (23.8)*	*414 (20.6)*
Nausea	511 (25.3)	201 (10.0)	199 (9.8)	137 (6.8)
Dry mouth	66 (3.3)	146 (7.3)	59 (2.9)	64 (3.2)
General disorders and administration site conditions	*270 (13.4)*	*241 (12.0)*	*404 (20.0)*	*229 (11.4)*
Application site pruritus	22 (1.1)	12 (0.6)	109 (5.4)	16 (0.8)
Fatigue	124 (6.2)	57 (2.8)	75 (3.7)	83 (4.1)

Table *continued*

Type of adverse event	No. (%)			
	Varenicline (*n* = 2016)	Bupropion (*n* = 2006)	NRT (*n* = 2022)	Placebo (*n* = 2014)
Infections and infestations	*533 (26.4)*	*475 (23.7)*	*495 (24.5)*	*506 (25.1)*
Nasopharyngitis	174 (8.6)	156 (7.8)	126 (6.2)	135 (6.7)
Upper respiratory tract infection	109 (5.4)	104 (5.2)	97 (4.8)	115 (5.7)
Nervous system disorders	*440 (21.8)*	*440 (21.9)*	*443 (21.9)*	*374 (18.6)*
Headache	245 (12.2)	186 (9.3)	233 (11.5)	199 (9.9)
Psychiatric disorders	*720 (35.7)*	*767 (38.2)*	*722 (35.7)*	*613 (30.4)*
Anxiety	132 (6.5)	169 (8.4)	138 (6.8)	120 (6.0)
Irritability	82 (4.1)	71 (3.5)	108 (5.3)	104 (5.2)
Abnormal dreams	201 (10.0)	131 (6.5)	251 (12.4)	92 (4.6)
Insomnia	189 (9.4)	245 (12.2)	196 (9.7)	139 (6.9)

EAGLES: Evaluating Adverse Events in a Global Smoking Cessation Study; n: total number of participants per treatment arm; NRT: nicotine replacement therapy.
Participants are only counted once per treatment for each row but may be counted in multiple rows.
All participants who received at least one partial dose of study treatment were included.
Treatment-related means during treatment plus 30 days.
Pfizer Food and Drug Administration advisory committee meeting briefing document, 2016 (*37*).

A 2020 Cochrane systematic review of antidepressants for smoking cessation included 87 studies involving bupropion SR treatment, 46 of which measured safety outcomes (*17*). The review concluded that bupropion SR was associated with an increased risk of adverse events (RR 1.14, 95% CI 1.11 to 1.18), although there was methodological and clinical variance between the included studies. Among 21 studies (10 625 participants) reporting serious adverse events, there was no clear evidence of increased risk (RR 1.16, 95% CI 0.90 to 1.48). However, smokers randomized to receive bupropion SR were more likely to report symptoms of anxiety (RR 1.42, 95% CI 1.21 to 1.67) and insomnia (RR 1.78, 95% CI 1.62 to 1.96) and experience psychiatric adverse events (RR 1.25, 95% CI 1.15 to 1.27). The authors took a different view of the EAGLES trial (*23*) and suggested that bupropion SR does increase the risk of psychiatric adverse events when considered broadly. They reached this conclusion by including psychiatric adverse events of any severity in their meta-analysis, whereas the EAGLES trial used a composite measure of only moderate and severe intensity psychiatric events in the primary analysis. The severity criteria for

the components of the composite endpoint in the EAGLES trial were imposed to minimize the inclusion of less clinically significant events, including some typically associated with nicotine withdrawal, and thus increase the specificity of the endpoint.

After the EAGLES trial, a study using a separate endpoint examined cardiovascular events in 8058 smokers (*38*). The primary endpoint was the time to the development of a major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) during treatment. The secondary endpoint was the occurrence of a major adverse cardiovascular event and other relevant cardiovascular events (e.g. new-onset or worsening peripheral vascular disease requiring intervention, coronary revascularization or hospitalization for unstable angina). The incidence of cardiovascular events during treatment and follow-up was low (< 0.5% for major adverse cardiovascular event; < 0.8% for a major adverse cardiovascular event plus other relevant cardiovascular events) and did not differ significantly by treatment. No significant differences were observed between treatment groups in time to cardiovascular events, blood pressure or heart rate. There was no significant difference in time to onset of a major adverse cardiovascular event for either varenicline or bupropion treatment versus placebo (varenicline: HR 0.29, 95% CI 0.05 to 1.68 and bupropion: HR 0.50, 95% CI 0.10 to 2.50). The authors concluded that there was no evidence that the use of smoking cessation pharmacotherapies increased the risk of serious cardiovascular adverse events during or after treatment.

Additional evidence (not in the application)

Not applicable.

WHO guidelines

WHO treatment guidelines for smoking cessation therapies are not currently available.

The 2019 WHO report on the global tobacco epidemic recommends offering help to quit tobacco use as one of the key measures in the MPOWER strategy (*6*). The report recognizes that both behavioural cessation support and nicotine-replacement and non-nicotine pharmacotherapies are effective in helping people to quit tobacco use. Combining both behavioural and pharmacotherapy interventions, however, is more effective and can double the chances of successfully quitting (*39*).

The 2003 WHO policy recommendations on smoking cessation and treatment of tobacco dependence note that a variety of behavioural and pharmacological therapies for smoking cessation have proved effective, but that no single approach should be emphasized to the exclusion of the others because

the therapies vary widely in their efficacy, acceptability, cost–effectiveness and their cost on an individual and population basis (*40*).

Costs/cost–effectiveness

The first economic analysis of bupropion for smoking cessation was conducted in 2000 (*41*) using data from a 1999 double-blind trial (*12*). The study examined 12-month outcome data from 893 smokers who were treated with either 9 weeks of bupropion (150 mg twice daily), nicotine patch, bupropion plus patch or placebo. The analysis followed a traditional cost–benefit approach to predict the net benefit to a payer after 1 year based on the effectiveness of the intervention (quit rates), the cost of the intervention, the cost of not quitting and the benefit of quitting. Compared with nicotine patch and combination therapy, 9 weeks of bupropion treatment was determined to be the most cost-beneficial treatment.
Another study developed an economic model to assess the costs and benefits to United States (US) payers of covering bupropion SR as a medication for smoking cessation (*42*). The model used a cohort of 100 000 employees and 60 000 dependents who were followed until retirement at 65 years or death at 85 years. If the costs of bupropion SR were covered, the overall decrease in health care costs over a 20-year period ranged from US$ 7.9 million to US$ 8.8 million; for every dollar spent covering smoking cessation, US$ 4.10–4.69 in health care costs were saved. For the employer scenarios, health care costs over 20 years decreased by US$ 8.3–14.0 million, and smoking-related indirect costs decreased an additional US$ 5.1–7.7 million; for every dollar spent covering smoking cessation, US$ 5.04–6.48 was saved.

An Australian study calculated the incremental cost–effectiveness ratio of bupropion and NRT compared with the current practice scenario (mass media campaigns and taxation on cigarettes which were widespread in Australia in 2000) (*43*). The outcome measure was disability-adjusted life year (DALY) averted in Australian dollars (AU$). DALYs averted is equivalent to the number of healthy life years gained. The authors concluded that providing bupropion to current smokers who are motivated to quit would cost AU$ 7900 (95% uncertainty interval AU$ 6000 to AU$ 10 500) for each DALY averted; NRT patches would cost AU$ 17 000 (AU$ 9000 to AU$ 28 000) for each DALY averted, with similar results even if used as a second-line treatment after failure to quit using bupropion. In addition, the authors noted that NRT and bupropion were more cost-effective than other medicines included in the public reimbursement list that are primarily focused on prevention, such as statins for lowering cholesterol.

Nicotine patch and bupropion SR were compared using the Global Health Outcomes simulation model with 20 years follow-up in Sweden (*44*). This study included a cohort of 612 851 male and 780 970 female smokers constructed to represent the 2001 population of Sweden aged 35 years and older.

This cost–utility study of a smoking cessation programme measured cost per quality-adjusted life year (QALY) gained by using bupropion SR and nicotine gum or nicotine patch. The incremental costs per QALY gained were relatively low for bupropion compared with nicotine patches, about € 725 for men and € 535 for women. The authors concluded bupropion was a cost-effective therapy for smoking cessation.

Researchers from Spain evaluated the cost–effectiveness of smoking cessation therapies, NRT and bupropion SR (*45*). For bupropion, the cost–effectiveness ratios at 5 years were € 70 939 and € 37 305 per death prevented and per year of life saved, respectively. When a 20-year time period was applied, the net savings were € 28 166 per death prevented and € 3265 per year of life saved. The cost–effectiveness ratios for both nicotine gum and patches were higher than that for bupropion. The authors concluded that bupropion treatment for 1 year would prevent a greater number of deaths than the alternative strategies (about 3000 deaths in a time period of 20 years) due to the decrease in the number of smokers.

In 2005, researchers from the Netherlands reported the results of a dynamic modelling study that examined minimal and intensive smoking interventions delivered by medical professionals (*46*). The study projected future gains in life years, QALYs, and savings in health care costs over 1 year, 10 years and on a permanent basis (up to 75 years). For treatment with bupropion SR or NRT, the intervention included counselling from a pulmonary nurse and physician, and either 9 or 12 weeks of pharmacotherapy. Overall, costs per life year and QALY gained were lower for bupropion treatment compared with NRT across all time periods. At 10 years, the costs per QALY gained for bupropion and NRT were € 3400 and € 4900, respectively. The authors noted that the cost–effectiveness ratios compared favourably to other cost-effective practices in the Netherlands, such as breast cancer screening (€ 4000 per life year gained) or influenza vaccination in elderly people (€ 1800 per life year gained).

A number of economic evaluations of the cost–effectiveness of varenicline compared with bupropion and NRT have been published based on the benefits of smoking cessation on outcomes (BENESCO) model, a Markov state-transition model developed by Pfizer, which includes health states for lung cancer, COPD, coronary heart disease, stroke and asthma exacerbations (*47–51*). These studies were completed in Europe and South Korea and found varenicline to be a cost-effective strategy despite the initial higher cost of varenicline.

Adopting a population level or public health view, then a variety of cessation strategies will be required to help smokers around the world. For example, a 2010 report to the Canadian health ministry concluded that pharmacotherapy, physician advice to quit, nursing interventions, hospital-based interventions and proactive telephone counselling were all likely to be

both effective and cost-effective in the short-term (*52*). Of these interventions, the report concluded that varenicline, bupropion and NRT, followed by physician advice to quit and nursing interventions to be the most effective strategies.

In a review of smoking cessation interventions to inform the development of national guidelines, researchers examined the affordability of such interventions according to country income level (*39*). The researchers used World Bank categories of low, middle and high income and estimated the incremental cost–effectiveness ratios for effective interventions for each category. The authors suggested that bupropion SR, similar to all medications for smoking cessation (except nortriptyline and cytisine), was affordable in middle- and high-income countries but not in low-income countries. However, additional research is necessary, including country-level analysis, before a conclusion can be reached that specific smoking cessation medications are not affordable relative to their benefits in low-income countries.

When assessing interventions and their costs, the evidence from economic studies strongly suggests that greater use of medications, including bupropion SR, generates net savings in tobacco-related health costs. The 2020 US Surgeon General's report concluded that the smoking cessation medications approved by the US Food and Drug Administration were cost-effective and increased the likelihood of successful quitting, and that combinations of therapies further increased the likelihood of quitting (*53*).

Availability

Bupropion SR is widely available globally, in originator and generic brands.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that smoking is a major public health threat worldwide and causes substantial harm to human health as a cause of numerous cancers, and cardiovascular and pulmonary diseases. Currently, the EML only includes nicotine replacement therapy for smoking cessation (chewing gum and transdermal patches).

The Expert Committee took into account the evidence shown in the application that there is high-certainty evidence that bupropion increases long-term smoking cessation rates as reported in a Cochrane review with more than 100 studies and that it is well tolerated overall. However, a synthesis of existing evidence also suggests an increased risk of adverse effects, particularly anxiety and agitation and these effects may increase the probability that people stop using the medicine.

The Expert Committee recognized that smoking cessation interventions are among the most cost-effective public health interventions. Moreover, there is sufficient evidence on the affordability of bupropion for smoking cessation, although not for low- and middle-income countries. The availability of different treatment options may enhance procurement capacity, lower prices and increase affordability through competition.

The Expert Committee also noted that no specialist training is required to prescribe or use the medicine. However, the success of medications for quitting smoking is improved when smokers are prepared to quit and receive quitting advice, counselling, and support from health care providers. The Expert Committee therefore noted that while the effectiveness of pharmacological interventions for smoking cessation is high, their success is dependent on a concomitant behavioural education approach such as counselling. In many countries, especially in low- and middle-income countries, the use of this approach as well as the strengthening of tobacco control policies are still not optimal.

The Expert Committee noted that bupropion was mentioned in the WHO Report on the Global Tobacco Epidemic 2019 as non-nicotine pharmacological intervention to help people to quit smoking.

Considering the body of evidence supporting the efficacy and tolerability of bupropion, the Expert Committee recommended the inclusion of bupropion for smoking cessation in the core list of the EML. However, considering the limited evidence on bupropion's affordability in low- and middle-income countries, mechanisms to estimate costs in these countries need to be established with ministries of health.

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Varenicline – addition – EML

Varenicline tartrate — ATC Code: N07BA03

Proposal

Addition of varenicline tartrate to the core list of the EML as an aid to smoking cessation in adults.

Applicant

Pfizer Inc., New York, United States of America

WHO technical department

Department of Health Promotion, Tobacco Free Initiative

EML/EMLc

EML

Section

24.5 Medicines for disorders due to psychoactive substance use

Dose form(s) & strength(s)

Tablet: 0.5 mg, 1 mg

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Varenicline has not previously been evaluated for inclusion on the EML.

Nicotine replacement therapy (NRT), as chewing gum or transdermal patch formulations, has been included on the EML since 2009. The Expert Committee recommended listing on the basis of the public health need, high-quality evidence of effectiveness, and acceptable safety and cost-effectiveness. Other formulations were not recommended for inclusion at the time because less evidence was available of comparative safety, effectiveness and cost in different populations (*1*).

Public health relevance (burden of disease)

Smoking is a leading cause of preventable death and disease worldwide and is a major global public health challenge. WHO estimates there are more than 1.3 billion tobacco users worldwide and about 80% of them live in low- and middle-income countries. While the prevalence of smoking has been declining across all income groups and in almost every region throughout the world, the average global smoking rate is still unacceptably high (19.2%) and about 8 million people still die every year from smoking-related diseases (*2*, *3*).

Furthermore, the global economic burden associated with smoking-attributable morbidity and mortality is substantial. One study estimated the global health care cost for smoking-related diseases at about US$ 467 billion, which is about 5.7% of total global expenditure on health care. When accounting for loss of productivity, the total economic burden of smoking is estimated at more than US$ 1 trillion a year (*4*).

The causal relationship between smoking tobacco and numerous disease processes, including cardiovascular disease (CVD), many types of cancer and pulmonary disease, is well established (*5*). For example, it is estimated that adults who smoke 20 cigarettes a day increase their relative risk of an ischaemic event by more than 50% and of the 9.4 million deaths attributed to coronary heart disease worldwide, about 18% are caused by smoking (*6*–*8*). In addition, smokers are at a 15–30 times higher risk of developing lung cancer compared with people who have never smoked, and are four times more likely to develop bladder cancer than people who do not smoke (*9*, *10*). Smoking is also the leading cause of chronic obstructive pulmonary disease (COPD) and 73% of disease-related mortality in high-income countries is attributable to smoking (*11*, *12*). Taken together, people who smoke may on average have a 10-year shorter life expectancy than people who have never smoked (*13*).

There are benefits to quitting smoking at almost any age, and people who successfully quit may significantly reduce their risk of developing or dying from smoking-related diseases. For example, 10 years after quitting smoking, the risk of developing lung cancer is 50% lower compared with people who continue to smoke; after 15 years of quitting, the risk of developing CVD is almost the same as someone who has never smoked. There are also short-term benefits to health that occur only weeks or months after stopping smoking, such as reduced frequency of cough and shortness of breath, as well as improved circulation and lung function (*2*, *5*).

The most common cessation approach taken by people who smoke is to make an unaided quit attempt, also known as quitting, so-called, cold turkey; it is estimated that about 4–8% of unaided quit attempts are successful (*2*, *5*). Several well established guidelines backed by high-quality evidence consider the combination of behavioural support and pharmacotherapy as the most effective

way to quit smoking in the short and long term (*14*, *15*). Although the efficacy of smoking cessation interventions varies, the combination of medication and behavioural support can as much as double a smoker's chances of quitting; the provision of medication or behavioural support alone have both been found superior to an unaided quit attempt (*2*, *14*). The uptake of interventions is dependent on both availability (i.e. access and cost) and on a smoker's preferences, which are likely to differ across social and cultural backgrounds. Therefore, the ability to offer a range of smoking cessation options is critical to facilitate maximum uptake and optimal treatment effectiveness (*2*).

Summary of evidence: benefits (from the application)

Two identically designed double-blind preauthorization clinical trials (A3051028 and A3051036) prospectively compared the efficacy of varenicline (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation (*16*, *17*). Participants received treatment for 12 weeks, followed by a 40-week non-treatment phase. Participants were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counselling at each weekly treatment visit. The primary endpoint of the two studies was the 4-week continuous abstinence rate confirmed by measurement of expired carbon monoxide (CO), from week 9 to week 12. At the primary endpoint, varenicline was shown to be statistically significantly superior to bupropion and placebo. After the 40-week non-treatment phase, a key secondary endpoint for both studies was the continuous abstinence rate at week 52. Continuous abstinence was defined as the proportion of all participants treated who did not smoke from week 9 to week 52 and did not have an exhaled CO measurement of > 10 ppm. The continuous abstinence rates during weeks 9–12 and 9–52 are shown in Table 16.

Table 16
Continuous abstinence during weeks 9–12 and 9–52 in preauthorization studies

Treatment groups	Study A3051028 (*16*) (*n* = 1025)		Study A3051036 (*17*) (*n* = 1027)	
	Weeks 9–12	Weeks 9–52	Weeks 9–12	Weeks 9–52
	Continuous abstinence rate (%)			
Varenicline	44.0	21.9	43.9	23.0
Bupropion	29.5	16.1	29.8	14.6
Placebo	17.7	8.4	17.6	10.3

Table *continued*

Treatment groups	Study A3051028 (*16*) (*n* = 1025)		Study A3051036 (*17*) (*n* = 1027)	
	Weeks 9–12	Weeks 9–52	Weeks 9–12	Weeks 9–52
	Odds ratio for continuous abstinence			
Varenicline vs placebo	3.85***	3.09***	3.85***	2.66***
Varenicline vs bupropion	1.93***	1.46	1.90***	1.77**

vs: versus.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Across both studies during active treatment, participant-reported outcome measures showed that craving and withdrawal were significantly reduced in participants randomized to varenicline compared with placebo. Varenicline also significantly reduced positive reinforcing effects of smoking, which can perpetuate smoking behaviour, in people who smoked during treatment compared with placebo.

Maintenance of abstinence

An open-label maintenance of abstinence study (A3051035) assessed the benefit of an additional 12 weeks of varenicline therapy on maintenance of abstinence in 1927 participants (*18*). Participants received varenicline 1 mg twice daily for 12 weeks. Participants who stopped smoking by week 12 were then randomized to receive either varenicline (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks. The study showed the benefit of an additional 12 weeks of treatment with varenicline 1 mg twice daily for the maintenance of smoking cessation compared with receiving a placebo after the first 12 weeks. The odds of maintaining abstinence at week 24, i.e. with an additional 12 weeks of treatment with varenicline, were 2.47 times higher than if receiving a placebo ($P < 0.001$). Superiority to placebo for continuous abstinence was maintained through week 52 (odds ratio (OR) 1.35; $P = 0.013$).

Flexible quit date

The effect of varenicline 1 mg twice daily in a flexible participant-selected quit date setting was assessed in a double-blind, placebo-controlled study of 651 people (study A3051095) (*19*). Participants were randomized 3:1 to varenicline ($n = 486$) or placebo ($n = 165$) for 12 weeks, followed by 12 weeks of post-treatment follow-up. Participants were instructed to select a quit date after the initial week of dose titration and before the clinical visit at the end of week 5 of

treatment. The rate of CO-confirmed abstinence during weeks 9 to 12 was 53.9% in participants treated with varenicline compared with 19.4% in participants treated with placebo (OR 6.03, 95% confidence interval (CI) 3.80 to 9.56). From week 9 to 24 the abstinence rate in the varenicline group was 35.2% compared with 12.7% in the placebo group (OR 4.45, 95% CI 2.62 to 7.55).

Varenicline retreatment

Varenicline was evaluated in a double-blind, placebo-controlled trial of 494 participants who had made a previous attempt to quit smoking with varenicline, and either did not succeed in quitting or relapsed after treatment (*20*). Participants were randomized 1:1 to varenicline 1 mg twice daily (n = 249) or placebo (n = 245) for 12 weeks of treatment and followed for up to 40 weeks after treatment. Participants included in the study had taken varenicline in the past in an attempt to stop smoking (for a total treatment duration of a minimum of 2 weeks), at least 3 months before entry into this study and had been smoking for at least 4 weeks. Participants treated with varenicline had an abstinence rate (CO-confirmed) of 45.0% during weeks 9 to 12, significantly higher than the 11.8% abstinence rate of participants treated with placebo (OR 7.08, 95% CI 4.34 to 11.55). From weeks 9 through 52, the abstinence rate of participants treated with varenicline was 20.1% compared with 3.3% in those treated with placebo (OR 9.00, 95% CI 3.97 to 20.41).

Gradual quitting approach

Varenicline was evaluated in a 52-week double-blind placebo-controlled study of 1510 participants who were not able or willing to quit smoking within 4 weeks but were willing to gradually reduce their smoking over a 12-week period before quitting (*21*). Participants were randomized to either varenicline 1 mg twice daily (n = 760) or placebo (n = 750) for 24 weeks and followed up after treatment through week 52. Participants were instructed to reduce the number of cigarettes smoked by at least 50% by the end of the first 4 weeks of treatment, followed by a further 50% reduction from week 4 to week 8 of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, participants continued treatment for another 12 weeks. Participants treated with varenicline had a significantly higher rate of continuous abstinence than those given placebo at weeks 15 through 24 (32.1% versus 6.9%, respectively; OR 8.74, 95% CI 6.09 to 12.53) and weeks 21 through 52 (27.0% versus 9.9%; OR 4.02, 95% CI 2.94 to 5.50).

Smokers with CVD

Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 703 people with stable, documented CVD (other than or in addition to hypertension) that had been diagnosed for more than 2 months (A3051049)

(*22*). Participants aged 35–75 years were randomized to varenicline 1 mg twice daily or placebo for a treatment period of 12 weeks and were then followed for 40 weeks after treatment. Participants treated with varenicline had a CO-confirmed abstinence rate of 47.3% during weeks 9 through 12, significantly higher than the 14.3% abstinence rate of participants treated with placebo (OR 6.05, 95% CI 4.13 to 8.86). From week 9 through 52, the abstinence rate of participants treated with varenicline was 19.8% compared with 7.4% in those treated with placebo (OR 3.19, 95% CI 1.97 to 5.18).

Smokers with COPD

Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 499 participants with mild to moderate COPD with postbronchodilator forced expiratory volume 1/forced vital capacity (FEV1/FVC) < 70% and FEV1 ≥ 50% of predicted normal value (*23*). Participants aged ≥ 35 years were randomized to varenicline 1 mg twice daily or placebo for a treatment period of 12 weeks and then were followed for 40 weeks after treatment. Participants treated with varenicline had a higher rate of CO-confirmed abstinence during weeks 9 through 12 than participants treated with placebo (42.3% versus 8.8%, respectively; OR 8.40, 95% CI 4.99 to 14.14) and from weeks 9 through 52 (18.6% versus 5.6%, respectively; OR 4.04, 95% CI 2.13 to 7.67).

Smokers with major depressive disorder

Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 525 participants with major depressive disorder without psychotic features who were on a stable dose of antidepressant treatment for at least 2 months and/or who had experienced a major depressive episode in the past 2 years and had been successfully treated (*24*). Participants aged 18–75 years were randomized to varenicline 1 mg twice daily or placebo for a treatment period of 12 weeks and then followed for 40 weeks after treatment. Participants treated with varenicline had a CO-confirmed abstinence rate of 35.9% during weeks 9 through 12, significantly higher than the 15.6% abstinence rate of participants treated with placebo (OR 3.35, 95% CI 2.16 to 5.21). From week 9 through 52, the abstinence rate of participants treated with varenicline was 20.3% compared with 10.4% in those treated with placebo (OR 2.36, 95% CI 1.40 to 3.98).

Smokers with and without history of psychiatric disorders

Varenicline was evaluated in a 24-week, double-blind, NRT (nicotine patch) and placebo-controlled, multicentre, parallel group study – the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial (*25*). The study was designed to assess the safety and efficacy of varenicline 1 mg twice daily and bupropion hydrochloride 150 mg twice daily for smoking cessation: the primary

safety focus was estimating the occurrence of neuropsychiatric adverse events and the main efficacy objectives were measuring continuous abstinence for weeks 9 to 12 and 9 to 24 in participants with and without a diagnosis of a psychiatric condition. The primary comparisons were varenicline versus placebo and bupropion versus placebo. NRT was included as an active control and study drugs were given via a triple dummy design, i.e. all participants took three drugs, which were either one active plus two placebo or all three were placebo. This allowed active versus active treatment comparisons as well as active versus placebo comparisons. The duration of active treatment was 12 weeks, followed by a non-treatment follow-up phase of an additional 12 weeks. In both groups and overall, all active treatments showed significantly greater efficacy in smoking cessation compared with placebo as measured at both weeks 9 to 12 (Table 17) and 9 to 24 (Table 18).

In addition, varenicline showed significantly greater efficacy compared with bupropion and compared with nicotine patch at both weeks 9 to 12 and 9 to 24. However, no significant differences in effectiveness were seen between bupropion and nicotine patch in either time period.

Table 17
Treatment comparison for continuous abstinence from tobacco use in smokers with and without psychiatric disorders, weeks 9–12

Treatment	Total	Group without psychiatric disorders	Group with psychiatric disorders
	Continuous abstinence, no./*n* (%)		
Varenicline	683/2037 (33.5)	382/1005 (38.0)	301/1032 (29.2)
Bupropion	460/2034 (22.6)	261/1001 (26.1)	199/1033 (19.3)
Nicotine patch	476/2038 (23.4)	267/1013 (26.4)	209/1025 (20.4)
Placebo	255/2035 (12.5)	138/1009 (13.7)	117/1026 (11.4)
Treatment comparisons	**Odds ratio (95% CI) for continuous abstinence**		
Primary comparisons			
Varenicline vs placebo	3.61 (3.07, 4.24)	4.00 (3.20, 5.00)	3.24 (2.56, 4.11)
Bupropion vs placebo	2.07 (1.75, 2.45)	2.26 (1.80, 2.85)	1.87 (1.46, 2.39)

Table *continued*

Treatment	Total	Group without psychiatric disorders	Group with psychiatric disorders
Secondary comparisons			
Nicotine patch vs placebo	2.15 (1.82, 2.54)	2.30 (1.83, 2.90)	2.00 (1.56, 2.55)
Varenicline vs bupropion	1.75 (1.52, 2.01)	1.77 (1.46, 2.14)	1.74 (1.41, 2.14)
Varenicline vs nicotine patch	1.68 (1.46, 1.93)	1.74 (1.43, 2.10)	1.62 (1.32, 1.99)
Bupropion vs nicotine patch	0.96 (0.83, 1.11)	0.98 (0.80, 1.20)	0.94 (0.75, 1.16)

CI: confidence interval; *n*: sample size; vs: versus.
Anthenelli RM, et al., 2016 (*25*).

Table 18
Treatment comparison for continuous abstinence from tobacco use in smokers with and without psychiatric disorders, weeks 9–24

Treatment	Total	Group without psychiatric disorders	Group with psychiatric disorders
	Continuous abstinence, no./*n* (%)		
Varenicline	445/2037 (21.8)	256/1005 (25.5)	189/1032 (18.3)
Bupropion	330/2034 (16.2)	188/1001 (18.8)	142/1033 (13.7)
Nicotine patch	320/2038 (15.7)	187/1013 (18.5)	133/1025 (13.0)
Placebo	191/2035 (9.4)	106/1009 (10.5)	85/1026 (8.3)
Treatment comparisons	**Odds ratio (95% CI) for continuous abstinence**		
Primary comparisons			
Varenicline vs placebo	2.74 (2.28, 3.30)	2.99 (2.33, 3.83)	2.50 (1.90, 3.29)
Bupropion vs placebo	1.89 (1.56, 2.29)	2.00 (1.54, 2.59)	1.77 (1.33, 2.36)

Table *continued*

Treatment	Total	Group without psychiatric disorders	Group with psychiatric disorders
Secondary comparisons			
Nicotine patch vs placebo	1.81 (1.49, 2.19)	1.96 (1.51, 2.54)	1.65 (1.24, 2.20)
Varenicline vs bupropion	1.45 (1.24, 1.70)	1.49 (1.20, 1.85)	1.41 (1.11, 1.79)
Varenicline vs nicotine patch	1.52 (1.29, 1.78)	1.52 (1.23, 1.89)	1.51 (1.19, 1.93)
Bupropion vs nicotine patch	1.04 (0.88, 1.24)	1.02 (0.81, 1.28)	1.07 (0.83, 1.39)

CI: confidence interval; *n*: sample size; vs: versus.
Anthenelli RM, et al., 2016 (*25*).

Healthy adolescent smokers

Varenicline was evaluated in a 12-week, randomized, double-blind, placebo-controlled, parallel group, dose ranging study with 40 weeks of follow-up in 312 healthy adolescent smokers aged 12–19 years (*26*). Participants were randomized 1:1:1 to either high-dose varenicline (1 mg twice daily or 0.5 mg twice daily for those weighing < 55 kg), low-dose varenicline (0.5 mg twice daily or 0.5 mg once daily for those weighing < 55 kg) or placebo. The study included a 12-week treatment period and a 40-week non-treatment follow-up period. All participants received < 10 minutes of age-appropriate cessation counselling at every study visit, in person or by telephone.

The study did not meet the primary endpoint of the cotinine-confirmed (urine) continuous abstinence rate from week 9 to week 12 in the overall study sample for either dose of varenicline compared with placebo. Analyses of secondary endpoints were consistent with the primary endpoint analysis. Results of a post hoc analysis of efficacy for a subset of participants 12–17 years were similar to those for the overall sample. Varenicline was well tolerated in this study population, with an adverse event profile similar to that observed in healthy adult smokers and no notable findings for neuropsychiatric adverse events.

Summary of evidence: harms (from the application)

Safety in randomized controlled studies

Eight phase II and III studies, which were conducted in smokers who were otherwise generally healthy, supported the initial authorization of varenicline.

The studies included a total of 5944 participants, with 3940 exposed to varenicline. In most of these studies the treatment period was 12 weeks while in one study it was 24 weeks and in another it was 52 weeks. Most of the studies included non-treatment follow-up to 1 year from start of treatment.

The two phase III pivotal studies of varenicline (*16*, *17*), included 692 participants treated with varenicline, 669 participants treated with bupropion and 684 participants treated with placebo. The most common adverse events in the varenicline treatment group were nausea (28.8% varenicline, 9.9% bupropion, 9.1% placebo), headache (14.2% varenicline, 11.1% bupropion, 12.4% placebo), insomnia (14.2% varenicline, 21.5% bupropion, 12.6% placebo) and abnormal dreams (11.7% varenicline, 5.7% bupropion, 4.5% placebo). In most cases, nausea occurred early in the treatment, was mild to moderate in severity and did not result in discontinuation of treatment. The occurrence of nausea decreased with time on varenicline (*27*).

Varenicline was studied in several postauthorization studies including a study on smokers with COPD (*23*), a study on generally healthy smokers who were allowed to select a flexible quit date between days 8 and 35 of treatment (*19*), a study of varenicline retreatment (*20*), a study on patients with stable CVD (*22*), a study on patients with stable schizophrenia or schizoaffective disorder (*28*), a study on patients with major depressive disorder (*24*), a postapproval safety outcome study on patients without or with a history of psychiatric disorder (EAGLES trial) specifically designed to assess the frequency of neuropsychiatric adverse events (*25*), and a study on smokers who used a gradual approach to quitting smoking (*21*). Postauthorization trials have also been conducted in specific countries or geographic regions, including Asia, Africa, the Middle East and South America (*29–32*).

The safety profile of varenicline was generally consistent across pre- and postauthorization studies. Table 19 shows the common adverse events in six preauthorization phase II-III studies (2005 pooled studies) and 15 pre- and postauthorization phase II-IV studies (2010 pooled studies). Table 20 shows common adverse events for the EAGLES study overall. Across all studies the most common adverts events reported in participants treated with varenicline and reported in a greater proportion of participants treated with varenicline than placebo were nausea, headache, abnormal dreams and insomnia.

Table 19

Most frequently reported treatment-related adverse events (by ≥ 5% of participants in any treatment group) in pooled study cohorts

Type of adverse event	No. (%)			
	2005 pooled studies		2010 pooled studies	
	Varenicline (*n* = 1983)	Placebo (*n* = 1209)	Varenicline (*n* = 4483)	Placebo (*n* = 2892)
Gastrointestinal disorders				
Constipation	118 (6.0)	27 (2.2)	235 (5.2)	68 (2.4)
Flatulence	130 (6.6)	34 (2.8)	196 (4.4)	69 (2.4)
Nausea	572 (28.8)	104 (8.6)	1221 (27.2)	241 (8.3)
Vomiting	59 (3.0)	8 (0.7)	146 (3.3)	25 (0.9)
General disorders and administration site conditions				
Fatigue	86 (4.3)	40 (3.3)	176 (3.9)	77 (2.7)
Nervous system disorders				
Dizziness	101 (5.1)	56 (4.6)	182 (4.1)	127 (4.4)
Dysgeusia	155 (7.8)	45 (3.7)	194 (4.3)	72 (2.5)
Headache	217 (10.9)	116 (9.6)	444 (9.9)	227 (7.8)
Psychiatric disorders				
Abnormal dreams	240 (12.1)	56 (4.6)	395 (8.8)	84 (2.9)
Insomnia	248 (14.3)	117 (9.7)	480 (10.7)	184 (6.4)

Includes adverse events up to 30 days after the last dose of the study drug.
2005 pooled studies included: A3051002, A3051007, A3051016, A3051028, A3051036 and A3051037.
2010 pooled studies included: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104 and A3051115.
Source: Food and Drug Administration review, 2011 (*33*).

Table 20

Most frequently reported treatment-related adverse events (by ≥ 5% of participants in any treatment arm), EAGLES trial

Type of adverse event	No. (%)			
	Varenicline (*n* = 2016)	Bupropion (*n* = 2006)	NRT (*n* = 2022)	Placebo (*n* = 2014)
Total with adverse event	**1503 (74.6)**	**1446 (72.1)**	**1436 (71.0)**	**1345 (66.8)**
Gastrointestinal disorders	*786 (39.0)*	*527 (26.3)*	*481 (23.8)*	*414 (20.6)*
Dry mouth	66 (3.3)	146 (7.3)	59 (2.9)	64 (3.2)
Nausea	511 (25. 3)	201 (10.0)	199 (9.8)	137 (6.8)
General disorders and administration site conditions	*270 (13.4)*	241 (12.0)	404 (20.0)	229 (11.4)
Application site pruritus	22 (1.1)	12 (0.6)	109 (5.4)	16 (0.8)
Fatigue	124 (6.2)	57 (2.8)	75 (3.7)	83 (4.1)
Infections and infestations	*533 (26.4)*	*475 (23.7)*	*495 (24.5)*	*506 (25.1)*
Nasopharyngitis	174 (8.6)	156 (7.8)	126 (6.2)	135 (6.7)
Upper respiratory tract infection	109 (5.4)	104 (5.2)	97 (4.8)	115 (5.7)
Nervous system disorders	*440 (21.8)*	*440 (21.9)*	*443 (21.9)*	*374 (18.6)*
Headache	245 (12.2)	186 (9.3)	233 (11.5)	199 (9.9)
Psychiatric disorders	*720 (35.7)*	*767 (38.2)*	*722 (35.7)*	*613 (30.4)*
Abnormal dreams	201 (10.0)	131 (6.5)	251 (12.4)	92 (4.6)
Anxiety	132 (6.5)	169 (8.4)	138 (6.8)	120 (6.0)
Insomnia	189 (9.4)	245 (12.2)	196 (9.7)	139 (6.9)
Irritability	82 (4.1)	71 (3.5)	108 (5.3)	104 (5.2)

EAGLES: Evaluating Adverse Events in a Global Smoking Cessation Study; n: total number of participants per treatment arm; NRT: nicotine replacement therapy.

Participants are only counted once per treatment for each row but may be counted in multiple rows.

All participants who received at least one partial dose of study treatment were included.

Treatment-related mean during treatment plus 30 days.

Source: Pfizer Food and Drug Administration advisory committee meeting briefing document, 2016 (*34*).

A 2016 Cochrane review and meta-analysis of placebo-controlled clinical trials of nicotine receptor partial agonists for smoking cessation included 39 trials involving varenicline treatment in 11 801 participants in a variety of populations and settings (*35*). The most frequent adverse events for smokers treated with varenicline was mild to moderate nausea, at rates between 24% and 29% in most studies. The other frequently reported adverse events included insomnia, abnormal dreams and headache. Meta-analyses of these four adverse events for varenicline versus placebo gave the following risk ratios (RRs) of: RR 3.27 (95% CI 3.00 to 3.55; 32 studies; 14 963 participants) for nausea; RR 2.12 (95% CI 1.88 to 2.38; 26 studies; 13 682 participants) for abnormal dreams; RR 1.49 (95% CI 1.35 to 1.65; 29 studies; 14 447 participants) for insomnia; and RR 1.17 (95% CI 1.07 to 1.29; 25 studies; 13 835 participants) for headache, with all differences being statistically significant.

The percentage of subjects experiencing at least one all-causality serious adverse event was low and similar between the varenicline and placebo groups in the 15 pooled preauthorization studies (3.2% versus 3.1%, respectively) (*33*). The most common adverse events leading to permanent treatment discontinuation were nausea, insomnia, depressed mood and depression.

In the EAGLES study, the percentages of participants with serious adverse events were similar across all treatment groups (1.9% varenicline, 2.4% bupropion, 2.3% NRT and 2.0% placebo) (*34*). The percentage of participants who discontinued treatment due to adverse events was also similar across treatment groups (8.2% varenicline, 8.8% bupropion and 8.0% NRT) and higher than the placebo group (6.1%). Higher percentages of participants in the group with psychiatric disorders discontinued study treatment due to adverse events compared with the group without psychiatric disorders (Table 21) (*25*).

Table 21
Adverse events leading to discontinuation of study treatment, EAGLES trial

Adverse event	No. (%)							
	Group without psychiatric disorders				Group with psychiatric disorders			
	Varenicline (*n* = 990)	Bupropion (*n* = 989)	Nicotine patch (*n* = 1006)	Placebo (*n* = 999)	Varenicline (*n* = 1026)	Bupropion (*n* = 1017)	Nicotine patch (*n*=1016)	Placebo (n=1015)
All causes of adverse events	57 (5.8)	75 (7.6)	74 (7.4)	29 (2.9)	109 (10.6)	101 (9.9)	88 (8.7)	93 (9.2)
Neuropsychiatric composite endpoint events	1 (0.1)	5 (0.5)	7 (0.7)	3 (0.3)	16 (1.6)	15 (1.5)	12 (1.2)	15 (1.5)

Anthenelli RM, et al., 2016 (*25*).

Neuropsychiatric safety

The EAGLES trial was a randomized, double-blind, triple-dummy, active and placebo-controlled study requested by the US Food and Drug Administration and conducted by Pfizer. The study evaluated the neuropsychiatric safety and efficacy of varenicline (1 mg twice daily) and bupropion sustained release (SR) (150 mg twice daily) compared with placebo and NRT (nicotine patch: 21 mg a day with tapering) for smoking cessation in 8144 participants with and without a history of psychiatric disorders (*25*). The study was also a postauthorization safety study in the European Union.

In each treatment arm, participants were divided into two groups – those without a psychiatric disorder and those with a current or past history of affective, anxiety, psychotic or personality disorders. The primary endpoint was a composite of moderate and/or severe adverse events comprising agitation, aggression, anxiety, delusions, depression, feeling abnormal, hallucinations, homicidal ideation, hostility, irritability, mania, panic, paranoia, psychosis, suicidal ideation, and suicidal behaviour and completed suicide.

In the overall study population, varenicline was not associated with an increased incidence of clinically significant neuropsychiatric adverse events for the composite primary endpoint. In the group without psychiatric disorders, the incidence of adverse events that comprised the primary endpoint was similar for varenicline and placebo (1.3% and 2.4%, respectively). In group without psychiatric disorders, the incidence of adverse events in the composite endpoint was higher for each of the active treatments compared with placebo (varenicline 6.5%, bupropion 6.7%, nicotine patch 5.2% and placebo 4.9%). However, in the psychiatric cohort, the 95% CI for all risk differences for treatment relative to placebo included zero.

One completed suicide was reported in the EAGLES study, which occurred in a participant treated with placebo in the group without psychiatric disorders. No completed suicides were reported in the group with psychiatric disorders. The frequency of suicidal ideation during the treatment period as well as during post-treatment follow-up was similar across the different treatments including placebo. Based on the Columbia-Suicide Severity Rating Scale, in the group without psychiatric disorders, ≤ 1% of participants across the different treatments reported suicidal ideation and/or behaviour during treatment and ≤ 30 days after treatment. However, in the group with psychiatric disorders, the percentages of participants reporting suicidal ideation and/or behaviour for the same time period were 3% for varenicline, 1% for bupropion, 2% for nicotine patch and 2% for placebo.

Several meta-analyses of neuropsychiatric adverse events in clinical studies with varenicline have shown similar results to the EAGLES trial. A systematic review and meta-analysis of 39 trials (10 761 participants) assessed

the risk of neuropsychiatric adverse events associated with varenicline (*36*). No increased risk was found for: aggression (OR 0.91, 95% CI 0.52 to 1.59); depression (OR 0.96, 95% CI 0.75 to 1.22); irritability (OR 0.98, 95% CI 0.81 to 1.17); suicidal ideation (OR 0.58, 95% CI 0.28 to 1.20); or suicide or suicide attempt (OR 1.67, 95% CI 0.33 to 8.57). Varenicline was associated with a reduced risk of anxiety compared with placebo (OR 0.75, 95% CI 0.61 to 0.93). However, the drug was associated with an increased risk of sleep-related adverse events, including insomnia (OR 1.56, 95% CI 1.36 to 1.78), abnormal dreams (OR 2.38, 95% CI 2.05 to 2.77) and fatigue (OR 1.28, 95% CI 1.06 to 1.55).

The 2016 Cochrane review (that included the EAGLES trial), included a meta-analysis of neuropsychiatric serious adverse events (*35*). The RR for depression was 0.94 (95% CI 0.77 to 1.14; 36 studies; 16 189 participants) and the RR for suicidal ideation was 0.68 (95% CI 0.43 to 1.07; 24 studies; 11 193 participants), both with non-statistically significant lower rates in the varenicline groups compared with placebo.

Overall, the data available show no evidence of an increased risk of clinically significant neuropsychiatric events with varenicline.

Cardiovascular safety

The risk for cardiovascular events in people taking varenicline has been studied in individual clinical trials as well as several meta-analyses. In a Pfizer randomized trial of 714 people with stable cardiovascular disease (*22*), the overall rate of cardiovascular events was low and all-cause and cardiovascular mortality was lower in people treated with varenicline than with placebo (0.3% versus 0.6%, respectively; difference −0.3% 95% CI, −1.3 to 0.7). However, non-fatal myocardial infarction and non-fatal stroke occurred more frequently in people treated with varenicline compared with people given a placebo (difference between groups: 1.1% and 0.3%, respectively), although the differences were not statistically significant.

In a randomized trial of varenicline versus placebo in 302 participants with acute coronary syndrome (*37*), major adverse cardiovascular events (defined as death, myocardial infarction or hospitalization for unstable angina) were reported in 4.0% of participants in the varenicline group and 4.6% of participants in the placebo group.

Cardiovascular events were also prospectively collected and adjudicated during, and as part of, a 28-week non-treatment follow-up to the EAGLES study, providing a total of 52 weeks of safety data (*38*). This study found no evidence that varenicline increased the risk of cardiovascular adverse events. However, because of the relatively low number of events overall, the upper bounds of the 95% CIs for hazard ratios and risk differences do not entirely rule out an association.

Meta-analyses of cardiovascular events in clinical trials on varenicline have produced inconsistent findings, with some analyses suggesting an increase in cardiovascular events with varenicline treatment (*39*,*40*) and others suggesting no effect of treatment with varenicline on cardiovascular events (*41*–*43*). Methodological differences, the size and duration of the studies, and the low number of cardiovascular events overall, likely contribute to the different results.

Additional evidence (not in the application)

Not applicable.

WHO guidelines

WHO treatment guidelines for smoking cessation therapies are not currently available.

The 2019 WHO report on the global tobacco epidemic recommends offering help to quit tobacco use as one of the key measures in the MPOWER strategy (*2*). The report recognizes that both behavioural cessation support and nicotine-replacement and non-nicotine pharmacotherapies are effective in helping people to quit tobacco use. Combining both behavioural and pharmacotherapy interventions, however, is more effective and can double the chances of successfully quitting (*44*).

The 2003 WHO policy recommendations on smoking cessation and treatment of tobacco dependence, note that a variety of behavioural and pharmacological therapies for smoking cessation have proved effective, but that no single approach should be emphasized to the exclusion of the others, because the therapies vary widely in their efficacy, acceptability, cost–effectiveness and their cost on an individual and population basis (*45*).

Costs/cost–effectiveness

Overall, smoking cessation therapy is considered to be a cost–effective intervention (*2*).

The benefits of smoking cessation on outcomes (BENESCO) model has been applied for various countries in Europe, South America, Asia and the USA. These analyses were generally conducted from the perspective of a health care payer using direct costs (drug acquisition costs, cost of a physician visit and brief counselling) and treatment-related costs for each morbidity. The model simulated a single quit attempt over a 1-year period and assessed the impact (i.e. cost associated with smoking cessation treatment and the development of smoking-attributable morbidity and mortality) over 2, 5, 10, 20, 50 years and/or a life-time (*46*). In several published evaluations, 12 weeks of therapy with varenicline was predicted to be a more cost-effective intervention from

the perspective of a health care payer over a 20-year or life-time period than bupropion, NRT or unaided quitting attempts in Belgium (*47*), Colombia (*48*), China Hong Kong Special Administrative Region (*49*), Czechia (*50*), Finland (*51*), Germany (*52*), Mexico (*53*), Netherlands (*54*), Scotland (*55*), Spain (*56*), Sweden (*57*), United Kingdom (*58*) and USA (*59*). The results are relatively consistent across countries with different levels of economic development, however most of the assessments have taken place in high- and middle-income countries.

Availability

Varenicline has received regulatory approval in 116 countries globally. With patent expiry, generic versions of varenicline may soon become available.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that smoking is a major public health threat worldwide and causes substantial health and economic harm, including different cancers. Currently, the EML only includes nicotine replacement therapy for smoking cessation (chewing gum and transdermal patches).

The Expert Committee considered the evidence shown in the application that the pooled risk ratio for continuous or sustained abstinence at 6 months or longer for varenicline at standard dosage versus placebo was significant. Moreover, varenicline was also significantly better than bupropion for this outcome. The pooled risk ratio for abstinence at 24 weeks was also significantly higher for varenicline than nicotine replacement therapy. As regards the safety of varenicline, neuropsychiatric effects are a concern. Still, the latest evidence from a randomized trial does not support a link between varenicline and these disorders, although people with past or current psychiatric illness may be at slightly higher risk of experiencing neuropsychiatric events than people without these disorders.

The Expert Committee was aware that smoking cessation interventions are among the most cost-effective public health interventions. Compared with other agents (bupropion and nicotine replacement therapy), the price of varenicline is higher and its use and availability in low- and middle-income countries are still limited. The Expert Committee noted that the availability of different treatment options may enhance procurement capacity, lower prices and increase affordability through competition.

The Expert Committee also noted that no specialist training is required to prescribe or use the medicine. However, the success of medications for quitting smoking is improved when smokers are prepared to quit, and receive

quitting advice, counselling and support from health care providers. The Expert Committee therefore noted that while the effectiveness of pharmacological interventions for smoking cessation is high, their success is dependent on a concomitant behavioural education approach such as counselling. In many countries, especially in low- and middle-income countries, the use of this approach as well as the strengthening of tobacco control policies are still not optimal.

The Expert Committee noted that varenicline was mentioned in the WHO Report on the Global Tobacco Epidemic 2019 as a non-nicotine pharmacological intervention to help people to quit smoking.

Considering the body of evidence supporting the efficacy and tolerability of varenicline, the Expert Committee recommended the inclusion of varenicline for smoking cessation in the core list of the EML. However, considering the limited evidence on the affordability of varenicline in low- and middle-income countries, mechanisms to estimate its costs in these countries need to be established with ministries of health.

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Section 29: MEDICINES FOR DISEASES OF JOINTS
29.2 Disease-modifying anti-rheumatic drugs (DMARDs)

Hydroxychloroquine – new indication – EML

Hydroxychloroquine **ATC Code: P01BA02**

Proposal

Inclusion of hydroxychloroquine on the complementary list of the EML for treatment of cutaneous lupus erythematosus with or without associated systemic lupus erythematosus.

Applicant

The International League of Dermatology Societies

WHO technical department

Not applicable

EML/EMLc

EML

Section

29.2 Disease-modifying anti-rheumatic drugs (DMARDs)

Dose form(s) & strength(s)

Solid oral dosage form: 200 mg (as sulfate)

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Hydroxychloroquine was added to the complementary list of the EMLc in 2011 for the treatment of systemic lupus erythematosus in children (*1*). It has not been previously considered by the Expert Committee for use in adults for any indication.

Public health relevance (burden of disease)

The global incidence of cutaneous lupus erythematosus ranges from 2.6 to 4.3 cases per 100 000 persons per year (*2–4*) and is similar to that of systemic lupus erythematosus, which ranges from 3.3 to 9.1 cases per 100 000 persons per year (*5*, *6*).

Active cutaneous lupus erythematosus can lead to damage of the skin (dyspigmentation and/or scarring) and is associated with considerable morbidity and impairment of quality of life (*6*, *7*). Patients with cutaneous lupus erythematosus have been reported to have worse quality of life than those with other common dermatological conditions, such as acne, non-melanoma skin cancer and alopecia (*8*). Factors related to poor quality of life in patients include female sex, presence of systemic lupus erythematosus, active skin disease, low income and low educational level suggesting that the disease burden is higher in low-resource settings (*8*, *9*).

Cutaneous lupus erythematosus most commonly presents with single or multiple plaques on the skin that heal by scarring and pigment loss. This is accompanied by scarring alopecia in the scalp, which leads to permanent hair loss. The condition may also be confined to the extremities such as fingertips, or the inflammation may extend to the deep dermis, where scarring is more severe.

It is estimated that about one in five people with widespread discoid lupus erythematosus or disseminated or acute cutaneous lupus erythematosus may subsequently develop systemic symptoms indicative of systemic lupus erythematosus (*4*, *10*).

Summary of evidence: benefits (from the application)

Cutaneous lupus erythematosus

In a randomized placebo-controlled trial of 103 patients with cutaneous lupus erythematosus, a greater proportion of patients who received hydroxychloroquine were determined to have "improved" or "remarkably improved" based on investigators' global assessment, compared with patients who received placebo (51.4% versus 8.7%, $P < 0.001$). Clinical improvement was assessed using the validated cutaneous lupus erythematosus disease area and severity index (CLASI). Patients treated with hydroxychloroquine had significantly improved CLASI scores from baseline after 16 weeks of treatment (10.1 versus 4.5; mean change –4.6, 95% confidence interval (CI) –6.1 to 3.1) (*11*).

A randomized, double-blind, multicentre study compared the efficacy of hydroxychloroquine and acitretin (a vitamin A derivative) in 58 patients with cutaneous lupus erythematosus (*12*). Similar efficacy was observed in the treatment groups based on the proportion of patients with overall improvement in cutaneous lupus erythematosus lesions (50% in the hydroxychloroquine

group versus 46% in the acitretin group). In the hydroxychloroquine group, there was complete clearing or marked improvement of erythema and of infiltration in 68% of patients, and of scaling/hyperkeratosis in 65% of patients. In the acitretin group, there was marked improvement or clearing of erythema in 42% of patients, of infiltration in 63% of patients and of scaling/hyperkeratosis in 60%.

A systematic review and meta-analysis of 31 studies published between 1965 and 2015 evaluated response rates of cutaneous lupus erythematosus subtypes to treatment with hydroxychloroquine and chloroquine (*13*). The overall response rate to both treatments was 63% (95% CI 55% to 70%). The evaluation of response to treatment was based on the definition used in each included study, mainly by the validated CLASI or according to study-specific criteria considering the size and number of lesions. For hydroxychloroquine, 1284 instances of treatment yielded an overall response rate to treatment of 61% (95% CI 50% to 71%), with significant statistical heterogeneity ($P < 0.001$ and $I^2 = 90\%$). In a meta-analysis of two studies allowing direct comparisons, hydroxychloroquine showed greater overall efficacy than chloroquine, however the difference was not statistically significant (odds ratio (OR) 1.48, 95% CI 0.98 to 2.23).

Systemic lupus erythematosus

A randomized, double-blind, placebo-controlled study evaluated the effect of discontinuing treatment with hydroxychloroquine in 47 patients with systemic lupus erythematosus who had been receiving this treatment for at least 6 months and had stable disease (*14*). The primary outcome measure was time to manifestation of clinical flare-up of systemic lupus erythematosus. The risk of systemic lupus erythematosus flare-ups (including major flare-ups) was 2.5 times higher (95% CI 1.08 to 5.58) at the end of the 6-months follow-up period in the discontinued (placebo) group compared with the hydroxychloroquine group. After an additional 3 years of follow-up, patients who continued on hydroxychloroquine had a reduced risk of experiencing a major disease flare-ups compared with patients who discontinued treatment; however, the difference was not significant (relative risk (RR) 0.43, 95% CI 0.17 to 1.12) (*15*).

A nested case–control study of 481 patients with systemic lupus erythematosus evaluated the effect of hydroxychloroquine on organ damage (*16*). A univariate analysis from this study found that hydroxychloroquine use was associated with a reduced risk of damage at 3 years after onset of disease (OR 0.33, 95% CI 0.15 to 0.74). In multivariate analyses, hydroxychloroquine was also associated with a lower risk of damage at 3 years (OR 0.34, 95% CI 0.13 to 0.84), after adjustment for disease activity, steroid dose, duration of disease and year of diagnosis.

Data from the multiethnic LUpus in MInorities, NAture versus nurture (LUMINA) study also showed that patients with systemic lupus erythematosus who did not receive hydroxychloroquine had higher damage scores and were significantly more likely to have renal disease or central nervous system disease (*17*). Furthermore, use of hydroxychloroquine was associated with a reduced risk of developing new damage. Data from this study also indicated that hydroxychloroquine had a beneficial effect on survival (OR for death 0.13, 95% CI 0.05 to 0.30) (*18*).

An observational prospective cohort study of 232 patients with systemic lupus erythematosus also found increased survival in patients who had received hydroxychloroquine or chloroquine (or both) compared with patients who never received these medicines (*19*). The cumulative 15-year survival was 95% for patients using hydroxychloroquine or chloroquine versus 68% for patients who had never used these medicines. However, the authors of this study acknowledged that potential confounders may have biased the findings. Finally, the use of hydroxychloroquine was also independently associated with greater survival in a population of patients with systemic lupus erythematosus with nephritis (*20*).

Summary of evidence: harms (from the application)

The most common adverse events associated with hydroxychloroquine include nausea (5%), diarrhoea (2%) and skin rash (2%) (*21*,*22*). Between 12 and 29% of patients treated with hydroxychloroquine discontinue treatment due to adverse events (*21*,*23*). Adverse events of moderate severity for hydroxychloroquine include severe headache and dizziness, tinnitus, and vertigo (*24*). Peripheral neuropathy has rarely been reported. Severe late-onset toxicity, including cardiotoxicity and myopathy, have also been rarely described in patients with cutaneous lupus erythematosus treated with hydroxychloroquine (*21*,*23*,*25*).

Hydroxychloroquine causes sodium and calcium channel blockade, which leads to membrane-stabilizing effects and may result in cardiac conduction disturbances with atrioventricular block, QRS interval widening and QT interval prolongation (*26*). Cardiac toxicity occurs rarely in patients with cutaneous lupus erythematosus, but the risk increases when hydroxychloroquine is used concurrently with other medicines that produce similar effects (*27*).

Hydroxychloroquine is also known to be associated with retinal toxicity (*28*,*29*), for which the dose regimen is an important risk factor. A retrospective case–control study found the overall prevalence of retinopathy associated with hydroxychloroquine to be 7.5%, but with variation dependant on daily consumption (OR 5.7, 95% CI 4.1 to 7.8 for daily doses > 5.0 mg/kg) and duration of use (OR 3.2, 95% CI 2.2 to 4.7 for duration of use > 10 years). For daily consumption of 4.0 to 5.0 mg/kg, the incidence of retinal toxicity was less than 2% within the first 10 years. Therefore, the maximum daily dose advocated

by the American Academy of Ophthalmology guidelines is 5.0 mg/kg actual body weight (*30*).

A population-based cohort study evaluated the risk of major congenital malformations in infants exposed to hydroxychloroquine during the first trimester of pregnancy (*31*). Babies exposed to hydroxychloroquine in utero had a higher rate of major congenital malformation than unexposed babies (54.8 per 1000 versus 35.3 per 1000; unadjusted RR 1.51, 95% CI 1.27 to 1.81). There were increases in the risk of oral clefts, respiratory anomalies and urinary defects, although estimates of relative risk were considered imprecise because of the relatively few events.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of cutaneous and systemic lupus erythematosus are not available.

Costs/cost–effectiveness

No published cost–effectiveness studies of hydroxychloroquine for the treatment of cutaneous lupus erythematosus were included in the application.

Availability

Hydroxychloroquine has wide global regulatory approval and is available in originator and generic brands.

Other considerations

European guidelines on cutaneous lupus erythematosus recommend using hydroxychloroquine as the first-line systemic treatment in all subtypes of cutaneous lupus erythematosus with severe or widespread skin lesions, particularly in patients with a risk of scarring and development of systemic lupus erythematosus (*32*). A daily dose of 5 mg/kg real body weight is recommended in the guidelines of the American Academy of Ophthalmology (*30*).

In recent guidelines of the European League Against Rheumatism (EULAR) for systemic lupus erythematosus, hydroxychloroquine is recommended for all patients with systemic lupus erythematosus, unless contraindicated, at a dose not exceeding 5 mg/kg real body weight (level of evidence 1a, grade of recommendation A) (*33*). However, in making this recommendation, the guidelines point out that studies of the efficacy of hydroxychloroquine in systemic lupus erythematosus have used a higher dose of 6.5 mg/kg.

Committee recommendations

The Expert Committee noted the reported prevalence of cutaneous lupus erythematosus and the fact that in its active form, it may lead to permanent damage (depigmentation and/or scarring) and is associated with considerable morbidity and impairment of quality of life.

The Committee also noted that the current listing for hydroxychloroquine on the Model List is limited to use in children for the treatment of systemic lupus erythematosus, and that ophthalmological monitoring is recommended as a condition for its use.

The Committee took into consideration that the approach to treating cutaneous lupus erythematosus is influenced by the subtype of disease and the presence of underlying systemic lupus erythematosus. The first-line therapy typically includes photoprotection and topical or intralesional corticosteroids, topical calcineurin inhibitors, systemic glucocorticoids and systemic antimalarial agents.

The Committee noted that hydroxychloroquine showed better efficacy than placebo in treatment of cutaneous lupus erythematosus, and similar efficacy and a better safety profile than acitretin and chloroquine. The main safety issues with hydroxychloroquine include cardiotoxicity and an increased risk of irreversible retinopathy, affecting up to 7% of patients who use higher doses and who continue treatment for a longer time (several years). The Committee acknowledged the dosage recommendations in international guidelines to minimize the risk of retinal toxicity.

The Expert Committee considered hydroxychloroquine to have an overall favourable benefit-to-risk ratio for use in the treatment of adults with cutaneous lupus erythematosus, to be generally affordable and widely available. Therefore, the Committee recommended its inclusion on the complementary list of the EML for this indication. In addition, the Committee also recommended hydroxychloroquine be included on the complementary list of the EML for the treatment of systemic lupus erythematosus in adults, given its beneficial effects on this condition. As was the case for listing on the EMLc, the Committee also recommended that the availability of ophthalmological monitoring be a condition for use in adults.

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29.3 Juvenile joint diseases

Anakinra – addition – EML and EMLc

Anakinra **ATC Code: L04AC03**

Proposal

Addition of anakinra to the complementary list of the EML and EMLc for the treatment of systemic-onset juvenile idiopathic arthritis (JIA) with macrophage activation syndrome.

Applicant

Paediatric Global Task Force for Musculoskeletal Health

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

29.3 Juvenile joint diseases

Dose form(s) & strength(s)

Injection: 100 mg/0.67 mL in prefilled syringe

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Anakinra had not previously been considered for inclusion on the Model Lists.

In 2007, acetylsalicylic acid (aspirin) was included on the first EMLc for the treatment of juvenile arthritis (*1*).

In 2019, the Expert Committee considered an application requesting inclusion of antitumour necrosis factor biological agents on the Model Lists for treatment of severe chronic inflammatory autoimmune disorders, including JIA (*2*). The Committee recognized that autoimmune disorders are highly debilitating and that there is a public health need for effective treatments for patients who do not respond to first-line treatments (e.g. methotrexate). On

the basis of the evidence presented and a positive benefit-to-harm profile of the medicines, the Committee recommended the addition of the antitumour necrosis factor antibody adalimumab, with a square box, with therapeutically equivalent alternatives limited to etanercept and infliximab for children (EMLc), and etanercept, infliximab, certolizumab pegol and golimumab for adults (EML). The Committee also recognized that these medicines have a substantial impact on the budget of health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to more market competition.

Public health relevance (burden of disease)

JIA is the most common chronic rheumatic disease of childhood, estimated to affect one in 1000 children (*3*). JIA is characterized by joint inflammation of more than 6 weeks' duration, with onset before the age of 16 years and absence of another underlying cause (*4*, *5*). It is an autoimmune, inflammatory joint disease, the cause of which remains poorly understood; both genetic and environmental factors are thought to contribute to its development (*6*). The age at onset is typically young, with a peak incidence between 1 and 3 years of age. The disease persists into adulthood in about 50% of cases (*7*). Worldwide, more than 2 million children are estimated to have JIA, with the greatest prevalence in Africa and Asia (*8*) where access to specialist care and treatment is limited (*9*) resulting in worse clinical outcomes (*10*). Untreated, JIA causes pain, joint damage and functional disability, and affects quality of life (*5*, *11*, *12*). JIA also results in children missing school, affects social and peer interactions which may cause long-term psychosocial difficulties and mental ill-health, and leads to higher unemployment in people with the condition than their healthy peers (*11*, *12*).

The International League of Associations for Rheumatology recognizes seven distinct subtypes of JIA (*4*, *13*). Systemic-onset JIA subtype is characterized by arthritis, fever, rash and systemic inflammation. Unlike other JIA subtypes, systemic-onset JIA is considered an autoinflammatory syndrome (*14*, *15*). The proportion of children with JIA who have systemic-onset JIA ranges from less than 10% to about 50% depending on the population, with higher rates reported in low-resource settings such as India (*16*). The condition is typically a chronic illness affecting young children – the age at onset is typically 1–5 years (*17*).

Uncontrolled inflammation in systemic-onset JIA carries significant risk of high morbidity and potential mortality from macrophage activation syndrome, an uncontrolled cytokine storm (*15*, *18*, *19*). Death rates for children with systemic-onset JIA are higher than for children with other JIA forms in the United Kingdom (standardized mortality ratio 8.3, 95% confidence interval (CI) 2.7 to 19.4 versus 1.7, 95% CI 0.5 to 4.0) (*20*).

The social implications are also important; 36% of caregivers reported that they had reduced their hours of work or stopped working due to their child's systemic-onset JIA, and they lost on average 25 days of work a year (*21*).

To prevent joint destruction, chronic pain and disability, as well as extra-articular complications such as blindness from uveitis (as a complication of JIA), the treatment paradigm for JIA has changed: earlier, more aggressive therapy is now the standard of care with early introduction of disease-modifying anti-rheumatic drugs (DMARDs) and, in many cases, biological agents (*5*, *22*). Notably, initial treatment of polyarticular disease in JIA with non-steroidal anti-inflammatory drugs alone is no longer recommended (*23*). Corticosteroids play a role in the early management of most forms of JIA, but their use in long-term health conditions is limited because of their side-effects (*24*), including growth failure, cataracts and osteoporosis (*12*).

Summary of evidence: benefits (from the application)

The application presented a review of the available evidence on the use of anakinra for systemic-onset JIA and macrophage activation syndrome in systemic-onset JIA, asserting that the most important way to treat macrophage activation syndrome in systemic-onset JIA is to control the underlying inflammation caused by systemic-onset JIA.

Anakinra in systemic-onset JIA

A single-centre prospective study in the Netherlands evaluated anakinra as first-line monotherapy in 42 patients (age range 3.9–11.8 years) with active systemic-onset JIA (*25*). The median time to achieve clinically inactive disease was 33 days. For children who had inactive disease at 3 months, anakinra was tapered and ultimately stopped. At 1 year, 76% of all the children had inactive disease, and 52% who had stopped receiving medication earlier continued to have inactive disease. Factors positively associated with inactive disease at 1 year included high neutrophil count at baseline and complete response after 1 month of anakinra treatment. After 5 years of follow-up, 96% of all the patients had inactive disease, and 75% continued to have inactive disease while not receiving medication. Articular or extra-articular damage was reported in < 5% of patients and only 33% received glucocorticoids. Treatment with anakinra was equally effective in systemic-onset JIA patients without arthritis at disease onset. The authors concluded that "treatment to target" (where disease activity is accurately monitored and clinical remission is actively pursued by regular adjustment of therapy (*26*), starting with first-line, short-course monotherapy with anakinra, is a highly effective strategy to induce and sustain inactive disease and to prevent damage from the disease and glucocorticoids.

A single-centre retrospective study in Italy evaluated 25 patients with systemic-onset JIA treated with anakinra for at least 6 months (*27*). The median

age at disease onset was 5.8 years and the median age at start of treatment was 7.3 years. Of note, 14 patients were receiving concomitant glucocorticoids, nine patients were receiving concomitant disease modifying antirheumatic drugs (methotrexate or ciclosporin), and six patients had previously received biological agents (etanercept, abatacept, infliximab). After 6 months of anakinra treatment, 14 patients (56%) had clinically inactive disease, reached at a median of 2.1 months after the start of treatment. Clinically inactive disease was maintained in all 14 patients at median follow up of 2.8 years. Nine patients were able to withdraw from anakinra and five continued with anakinra monotherapy. No cases of macrophage activation syndrome were observed during anakinra treatment.

An international multicentre series analysed the use of anakinra as first-line disease-modifying therapy in 46 children with systemic-onset JIA (*28*). Of 46 patients meeting the inclusion criteria, anakinra monotherapy was used in 10 patients (22%), 21 received anakinra plus corticosteroids, five received anakinra plus DMARDs and 10 received anakinra plus corticosteroids and DMARDs. Outcomes were evaluated after a median follow-up of 14.5 months. Fever and rash resolved within 1 month in more than 95% of patients, while C-reactive protein and ferritin normalized within this time in more than 80% of patients. Active arthritis persisted at 1 month in 39% of patients, at 3 months in 27% and at more than 6 months of follow-up in 11% of patients. About 60% of patients, including eight of 10 receiving anakinra monotherapy, attained a complete response without escalating therapy. Eleven episodes of macrophage activation syndrome (in nine patients) were observed, six episodes at presentation and five episodes after starting anakinra during the study. Anakinra effectively managed five out of the six cases of macrophage activation syndrome at presentation; increasing doses of anakinra and additional agents such as steroids and ciclosporin A were used to control these episodes.

A retrospective case series from the United States of America (USA) evaluated the effect of anakinra on disease activity and corticosteroid dose in 33 patients with systemic-onset JIA (*29*). The median duration of systemic-onset JIA before treatment was 29 months and most patients had used more than one other medication before starting anakinra: prednisone (94%), methotrexate (76%), tumour necrosis factor inhibitors (61%), ciclosporin (36%) and cyclophosphamide (6%). Anakinra treatment was associated with reduction in corticosteroid dosage and erythrocyte sedimentation rate, and increases in haemoglobin and albumin, all indicators of response to therapy. Large joint arthritis counts decreased but not small joint counts after 3–4 months. More significant decreases in erythrocyte sedimentation rates from pre- to post-treatment (1–2 months) were seen in patients on high doses of anakinra than those on low doses, implying a dose–response effect. Fever and rash, present in seven cases before treatment, resolved in all cases. Eight patients had periods of arthritis, one developed macrophage activation syndrome and another Epstein–Barr virus infection.

A single-centre series study reported on four patients who received anakinra as first-line therapy for systemic-onset JIA (*30*). The median age of the patients was 4.6 years (range 2.75–9.25 years). The mean follow-up time was 13.5 months (range 2–50 months). Anakinra was started at doses from 1.5 to 4 mg/kg for a median duration of 3 (range: 3–18) months. Two patients responded to anakinra monotherapy; two cases required corticosteroids. Normalized body temperature and the absence of evanescent rashes were achieved after a median of 4 (range: 2–10) days. The data suggest rapid efficacy of anakinra in early systemic-onset JIA with reduced treatment-related side-effects.

Macrophage activation syndrome in systemic-onset JIA

A single-centre study evaluated the use of anakinra to treat macrophage activation syndrome in 15 paediatric patients (*31*), 13 with systemic-onset JIA and two with other autoinflammatory diseases. Nineteen episodes of macrophage activation syndrome were observed in the 15 patients. Anakinra (2 mg/kg a day) was started within a median of 1 day of admission. Clinical symptoms resolved within a median (minimum–maximum) of 2 (1–4) days of the introduction of anakinra and laboratory findings normalized within a median of 6 (4–9) days. Steroid treatment was stopped within a median of 10 (4–13) weeks of starting anakinra. Patients were followed for a median of 13 (6–24) months. Two patients developed recurrent macrophage activation syndrome episodes when the anakinra dose was reduced, while the other patients achieved remission.

A retrospective case series reported on 12 children with macrophage activation syndrome (eight due to systemic-onset JIA) in whom steroids, ciclosporin A and intravenous immunoglobulin were not working (*32*). Five patients required intensive care. All patients achieved remission of macrophage activation syndrome after addition of anakinra within a median of 13 (range 2–19) days. Corticosteroids were discontinued by 6 weeks in seven patients. Patients were followed for a median of 22 (2–40) months and all were in remission for macrophage activation syndrome at the final follow-up with excellent control of the underlying rheumatic disease.

Summary of evidence: harms (from the application)

Anakinra is used in systemic-onset JIA, macrophage activation syndrome and other autoinflammatory diseases such as cryopyrin-associated periodic fever syndrome (CAPS), rheumatoid arthritis and gout. In general, anakinra has a satisfactory safety profile.

An international multicentre series described the use of anakinra to treat 46 children with systemic-onset JIA (*28*). Adverse events observed included injection site reactions (*20* cases), serious infections (three cases), elevation of liver enzymes (two cases), hepatitis (one case), and mild asymptomatic neutropenia (one case).

A prospective, open-label, single-centre, clinical cohort study investigated the efficacy and safety of anakinra treatment for up to 5 years in 43 patients with cryopyrin-associated periodic fever syndrome. Safety was evaluated using adverse-event reports, laboratory assessments, vital signs and diary reports (*33*). In total, 1233 adverse events were reported during the study, with a yearly rate of 7.7 adverse events per patient. The event rate decreased over time, and dose escalation during the study did not affect the frequency of adverse events. The most frequently reported adverse events were the typical disease symptoms of cryopyrin-associated periodic fever syndrome such as headache and arthralgia. Injection site reactions occurred mainly during the first month of anakinra treatment. In total, 14 patients experienced 24 severe adverse events, all of which resolved during the study period. The most commonly reported serious adverse events were infections (13 events in seven patients; seven events in three patients younger than 2 years). The most common infections were pneumonia (three patients) and gastroenteritis (two patients). Anakinra had similar safety profiles in adults and children.

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the treatment of systemic-onset JIA and macrophage activation syndrome in systemic-onset JIA are not currently available.

Costs/cost–effectiveness

No comparative cost–effectiveness studies of anakinra in systemic-onset JIA are available.

Availability

Anakinra does not yet have regulatory approval as a treatment for macrophage activation syndrome. It has regulatory approval for the treatment of systemic-onset JIA in the following countries: Australia, Austria, Belgium, Bulgaria, Canada, Cyprus, Czechia, Denmark, Estonia, Finland, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden, United Kingdom and the USA.

Other considerations

Diagnosis and management

The diagnosis of macrophage activation syndrome in systemic-onset JIA is based on defined criteria (*19*) validated in clinical practice (*34*, *35*). Macrophage

activation syndrome is often triggered by infection, a particular concern in low-resource countries. It is also a life-threatening "cytokine storm" with a high risk of death (*36*). Access to specialist paediatric rheumatologists, multidisciplinary teams and treatments are challenges in many low-resource countries. Such inequity further contributes to the burden of disease and long-term disability (*37*). The diagnosis of macrophage activation syndrome and evaluation of its severity, and monitoring of response to treatment are assessed using blood markers of inflammation (C-reactive protein and full blood counts) as well as specific markers of macrophage activation syndrome (ferritin, triglycerides, liver function tests and clotting profiles) (*34*, *35*). Monitoring anakinra treatment follows the routine monitoring of systemic-onset JIA in acute disease flare-up, concomitant infection or where macrophage activation syndrome is suspected.

Tuberculosis risk

Awareness of the risk of tuberculosis in patients treated with anakinra or tocilizumab and other biological DMARD medications is of particular importance in low resource settings with high rates of tuberculosis. This awareness is emphasized in consensus statements on JIA care in low-resource settings as level 3b evidence, strength A statement with 100% consensus (*37*). It is also recommended that patients with JIA with a positive tuberculosis test should receive appropriate prophylaxis for tuberculosis (as per current national and/or international guidelines) at the start of biological therapy, during biological therapy and when a previously negative purified protein derivative test converts to positive at the mandatory annual tuberculosis screening, and if they have a new exposure to tuberculosis.

Committee recommendations

The Expert Committee noted that macrophage activation syndrome is a rare but serious condition involving excessive immune activation that can occur in children with systemic-onset juvenile idiopathic arthritis (JIA), and that it is associated with high short-term mortality, especially if untreated.

The Committee noted anakinra has not been approved for this indication by the European Medicines Agency or the US Food and Drug Administration. However, anakinra is suggested as an initial therapeutic option for patients with suspected macrophage activation syndrome according to the 2013 JIA guideline of the American College of Rheumatology guidelines (weak recommendation).

The Committee acknowledged that other treatments for systemic-onset JIA recommended in guidelines and used in clinical practice include corticosteroids and disease-modifying anti-rheumatic agents (DMARDs), such as methotrexate, antitumour necrosis factor alpha agents (e.g. etanercept, adalimumab), Janus kinase inhibitors (e.g. tofacitinib) and anti-interleukin-6 receptor antibodies (e.g. tocilizumab, canakinumab). The Committee

acknowledged that management of systemic-onset JIA with DMARD treatment has the potential to minimize the severe side-effects of corticosteroids and noted that antitumour necrosis factor agents were included on the EML and EMLc for juvenile idiopathic arthritis in 2019.

The Committee noted that the application reported data only from uncontrolled cohort studies or case series, most enrolling a small number of patients. The Committee agreed that extrapolating clinical benefits and potential harms of anakinra and comparing anakinra to other potentially relevant therapeutic alternatives based on this type of evidence was difficult. The Committee accepted that there may not be alternatives to quasi-experimental studies on macrophage activation syndrome given the rarity of the disease, but that this was not the case for systemic-onset JIA.

The Committee also noted that anakinra is often a highly priced medicine, with potentially important limitations in accessibility and affordability at the country level. The Committee also acknowledged the limitations in availability of specialist paediatric rheumatologists in some lower-resource settings.

The Expert Committee therefore did not recommend the listing of anakinra for the treatment of systemic-onset JIA and macrophage activation syndrome because of the uncertainty in the estimates of clinical benefit and concerns about affordability and access to specialist medical services.

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Tocilizumab – addition – EML and EMLc

Tocilizumab **ATC Code: L04AC07**

Proposal

Addition of tocilizumab on the complementary list of the EML and EMLc for the treatment of systemic-onset juvenile idiopathic arthritis (JIA).

Applicant

Paediatric Global Musculoskeletal Task Force

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

29.3 Juvenile joint diseases

Dose form(s) & strength(s)

Injection (subcutaneous): 162 mg/0.9 mL
Injection (intravenous): 80mg/4 mL, 200 mg/10 mL, 400 mg/20 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Tocilizumab had not previously been considered for inclusion on the Model Lists.

In 2007, acetylsalicylic acid (aspirin) was included on the first EMLc for the treatment of juvenile arthritis (*1*).

In 2019, the Expert Committee considered an application requesting inclusion of antitumour necrosis factor biologicals to the Model Lists for treatment of severe chronic inflammatory autoimmune disorders, including JIA (*2*). The Committee recognized that autoimmune disorders are highly debilitating and that there is a public health need for effective treatments for patients who do not respond to first-line treatments (e.g. methotrexate). On the basis of the

evidence presented and a positive benefit-to-harm profile of the medicines, the Committee recommended the addition of the antitumour necrosis factor antibody adalimumab, with a square box, with therapeutically equivalent alternatives limited to etanercept and infliximab for children (EMLc), and etanercept, infliximab, certolizumab pegol and golimumab for adults (EML). The Committee also recognized that these medicines have a substantial impact on the budget of health systems. However, the availability of several therapeutically equivalent alternatives, and the increasing availability of biosimilar products could lead to more market competition.

Public health relevance (burden of disease)

JIA is the most common chronic rheumatic disease of childhood, estimated to affect one in 1000 children (*3*). JIA is characterized by joint inflammation of more than 6 weeks' duration, with onset before the age of 16 years and absence of another underlying cause (*4*, *5*). It is an autoimmune, inflammatory joint disease, the cause of which remains poorly understood; both genetic and environmental factors are thought to contribute to its development (*6*). The age at onset is typically young, with a peak incidence between 1 and 3 years of age. The disease persists into adulthood in about 50% of cases (*7*). Worldwide, more than 2 million children are estimated to have JIA, with the greatest prevalence in Africa and Asia (*8*), where access to specialist care and treatment is limited (*9*) resulting in worse clinical outcomes (*10*). Untreated, JIA causes pain, joint damage and functional disability, and affects quality of life (*5*, *11*, *12*). JIA also results in children missing school, affects social and peer interactions which may cause long-term psychosocial difficulties and impaired mental health, and leads to higher unemployment in people with the condition than their healthy peers (*11*, *12*).

The International League of Associations for Rheumatology recognizes seven distinct subtypes of JIA (*4*, *13*). Systemic-onset JIA subtype is characterized by arthritis, fever, rash and systemic inflammation. Unlike other JIA subtypes, systemic-onset JIA is considered an autoinflammatory syndrome (*14*, *15*). The proportion of children with JIA who have systemic-onset JIA ranges from less than 10% to about 50% depending on the population, with higher rates reported in low-resource settings such as India (*16*). The condition is typically a chronic illness affecting young children – the age at onset is typically 1–5 years (*17*).

Uncontrolled inflammation in systemic-onset JIA carries significant risk of high morbidity and potential mortality from macrophage activation syndrome, an uncontrolled cytokine storm (*15*, *18*, *19*). Death rates for children with systemic-onset JIA are higher than for children with other JIA forms in the United Kingdom (standardized mortality ratio 8.3, 95% confidence interval (CI) 2.7 to 19.4 versus 1.7, 95% CI 0.5 to 4.0) (*20*).

The social implications are also important; 36% of caregivers reported that they had reduced their hours of work or stopped working due to their child's systemic-onset JIA, and they lost on average 25 days of work a year (*21*).

To prevent joint destruction, chronic pain and disability, as well as extra-articular complications such as blindness from uveitis (as a complication of JIA), the treatment protocol for JIA has changed: earlier, more aggressive therapy is now the standard of care with early introduction of disease-modifying anti-rheumatic drugs (DMARDs) and, in many cases, biological agents (*5*, *22*). Notably, initial treatment of polyarticular disease in JIA with non-steroidal anti-inflammatory drug alone is no longer recommended (*23*). Corticosteroids play a role in the early management of most forms of JIA, but their use in long-term health conditions is limited because of their side-effects (*24*), including growth failure, cataracts and osteoporosis (*12*).

Summary of evidence: benefits (from the application)

The criteria for response defined by the American College of Rheumatology Pediatric (ACR Pedi) are: at least a 30% improvement from baseline in three of six variables for juvenile arthritis, with no more than one remaining variable worsening by > 30%. The ACR Pedi 50, 70, 90 and 100 response definitions require 50%, 70%, 90% and 100% improvement, respectively, in at least three core variables with no more than one variable worsening by > 30% (*25*). These criteria are the reference standard for the assessment of response to therapy in JIA. The ACR Pedi 30 was adapted for use in clinical trials in systemic-onset JIA by adding, besides the six core variables, the demonstration of the absence of spiking fever (> 38.0 °C) in the week preceding the evaluation (*26*).

Randomized trials

A randomized, double-blind, placebo-controlled, withdrawal phase III trial evaluated the efficacy and safety of tocilizumab in 56 children aged 2–19 years with systemic-onset JIA not responding to DMARDs and biological agents (*27*). After an initial open-label lead-in phase where all participants were administered tocilizumab (three intravenously administered doses of 8 mg/kg every 2 weeks), ACR Pedi 30, 50 and 70 responses were achieved by 51 (91%), 48 (86%) and 38 (68%) of patients, respectively. Thereafter, 43 participants who had achieved both an ACR Pedi 30 response and C-reactive protein concentrations of less than 5 mg/L were randomized to receive tocilizumab or placebo in a double-blind phase for 12 weeks (administration of placebo or tocilizumab 8 mg/kg every 2 weeks). Patients who remained on tocilizumab in the double-blind phase had sustained improvement in clinical measures of effectiveness and well-being. In contrast, most of those in the placebo group (18/23 patients) required rescue treatment. After the lead-in and double-blind phases, corticosteroid doses were

reduced by at least 50% in most patients. Patients responding to tocilizumab and needing further treatment were then enrolled in an open-label extension phase for at least 48 weeks. By week 48 of the open-label extension phase, ACR Pedi 30, 50 and 70 responses were achieved by 47 (98%), 45 (94%), 43 (90%) of 48 patients, respectively.

The multicentre, randomized TENDER trial evaluated the efficacy of tocilizumab compared with placebo in 112 children aged 2–17 years with persistent systemic-onset JIA for at least 6 months and inadequate response to non-steroidal anti-inflammatory drugs and glucocorticoids (*26*). Patients were randomized in a 2:1 ratio to either tocilizumab (12 mg/kg if weighing < 30 kg or 8 mg/kg if weighing ≥ 30 kg) or placebo intravenously every 2 weeks for 12 weeks. After 12 weeks, the primary endpoint of ACR Pedi 30 response and absence of fever was met by 85% (64/75) in the tocilizumab group and 24% (9/37) in the placebo group ($P < 0.001$). In this study, 84% of the patients in the treatment group had previously received a biological agent, including 55% who had received interleukin-1 inhibitors and 73% who had received antitumour necrosis factor agents. In the open-label extension phase, which included 73 patients randomized to receive tocilizumab and 37 patients randomized to placebo, 59% had an ACR Pedi 90 response and an absence of fever at week 52.

Other studies

A German registry study reported that over a 5-year period, 46 of 200 patients with systemic-onset JIA were treated with tocilizumab (*28*). A clinical response rate (defined as no symptoms and typical inflammatory markers) of 35% was reported in the first 12 weeks of treatment, and inactive disease/remission on medication (as defined in the Wallace criteria (*29*)) was reported in 75% of patients after 1 year.

Safety and effectiveness of tocilizumab were evaluated in 417 patients with systemic-onset JIA in real-world clinical settings in Japan (*30*). Fever and rash symptoms decreased from baseline to week 52 (from 54.6% to 5.6% and from 43.0% to 5.6%, respectively). At 4 weeks, 8 weeks and 52 weeks, 90.5%, 96.2% and 99.0% of patients, respectively, achieved normal levels of C-reactive protein (< 0.3 mg/dL).

A posthoc analysis of 83 patients treated with tocilizumab in the phase III TENDER trial (see above) reported significant catch-up growth (above normal height velocities of 6.6 cm/year), normalization of levels of insulin growth factor-1 and bone balance improvement favouring bone formation (*31*). In another analysis of 45 patients treated with tocilizumab, 38 (84%) had a clinical response with improved growth by week 144 (*32*). A significant improvement in change in height velocity mean standard deviation score was seen from 1 year before to 1 year after baseline (mean (standard deviation): –6.0 (4.0) to –2.5 (3.9);

$P = 0.006$). Reduction in corticosteroid exposure was significantly associated with improvement in height velocity. Eight patients (18%) reduced their corticosteroid dose by 50% and 26 (58%) reduced their corticosteroid dose by 70%.

A small single-centre cohort study assessed clinical outcomes and patient satisfaction in 39 children with JIA treated with intravenous tocilizumab, all of whom were offered a switch from intravenous to subcutaneous tocilizumab formulation. Of the nine patients who accepted the switch, eight were satisfied with subcutaneous administration in terms of quality of life, school success and reduced school absenteeism (*33*). Three months after switching, no deterioration in clinical (active joint counts, physician or patient visual analogue scale for pain and Juvenile Arthritis Disease Activity Score 71) and laboratory parameters (C-reactive protein, white blood cell count and platelets) was observed.

Comparison with other treatments

A systematic review and network meta-analysis of five trials evaluating biological agents for treatment of systemic JIA indicated that canakinumab and tocilizumab were more effective in achieving a clinical response than rilonacept, an interleukin-1 inhibitor (*34*). Specifically, people treated with rilonacept were less likely to respond than people treated with canakinumab (odds ratio (OR) 0.10, 95% CI 0.02 to 0.08) or tocilizumab (OR 0.12, 95% CI 0.03 to 0.44). However, the evidence was considered low quality because of indirect comparisons and heterogeneous eligibility criteria and study designs of the included trials.

A systematic review of 25 studies (including nine randomized controlled trials) investigated biological agents for treatment of JIA on over 4000 patients, including 1185 patients with systemic-onset JIA (*35*). The review concluded that systemic-onset JIA appeared to be less responsive to etanercept than tocilizumab over 12 weeks (etanercept: ACR Pedi 30 58–78% and tocilizumab: ACR30 85%). More similar responses were seen after 12 months (etanercept: ACR Pedi 30 83–100% and tocilizumab: ACR Pedi 30 87–98%).

A retrospective study of 245 patients with systemic-onset JIA treated with biological agents between 2000 and 2015 included in a German registry evaluated efficacy and safety of tocilizumab, interleukin 1 inhibitors (anakinra, canakinumab) and etanercept (*36*). ACR Pedi 30, 50, 70 and 90 responses were achieved more often over 24 months in patients treated with tocilizumab or interleukin 1 inhibitors than in those treated with etanercept. People who received tocilizumab were also less often treated with systemic glucocorticoids than those who received etanercept (44% versus 83%; $P < 0.001$). However, the characteristics of the patients treated with the various medicine were notably different (partly owing to the changing availability of different medicines over time) and, despite the use of a propensity score model based on, residual confounding cannot be excluded.

Summary of evidence: harms (from the application)

In the double-blind phase of the TENDER trial that randomized 75 patients with systemic-onset JIA to tocilizumab and 37 to placebo the most common adverse events were infections, with 60 events in the tocilizumab group (of which two were classified as severe; 3.4 infections per patient year) compared with 15 in the placebo group (none severe; 2.9 events per patient year). In the double-blind and extension periods combined, including patients initially assigned to placebo who made the transition to open-label tocilizumab, there were 39 serious adverse events (equivalent to 0.25 per patient year), including 18 serious infections (11 per 100 patient years). Adverse events led to discontinuation of tocilizumab in six patients (for two because of elevated aminotransferase levels). There were three episodes of macrophage activation syndrome, all of which resolved. Three deaths occurred during treatment, including one from probable streptococcal sepsis (*26*).

A postmarketing surveillance study in Japan followed 417 patients treated with tocilizumab in the real-world setting for 52 weeks (*30*). The study reported overall adverse event and serious adverse event rates of 224.3 per 100 patient years and 54.5 per 100 patient years, respectively, which were higher than previously reported in clinical trials. Adverse events leading to discontinuation of tocilizumab occurred in 4.1% of patients. The most common adverse events reported were infections (69.8 per 100 patient years). There were 74 serious infections in 55 patients, equivalent to 18.2 severe infections per 100 patient years. Two deaths occurred in the 52 weeks, one due to vasculitis with cardiac failure, and one due to Pseudomonas infection, interstitial lung disease and sepsis. In the case of seven episodes of macrophage activation syndrome (out of a total of 26 macrophage activation syndrome events), infections were thought to contribute.

In a German registry study of 46 patients treated with tocilizumab, adverse events were seen in 11/46 (24%) patients and severe adverse event in 2/46 (4%) patients. No cases of macrophage activation syndrome or death were reported. Discontinuation of treatment due to adverse events was reported in 5/46 (11%) patients (*28*).

Comparative safety

A German registry study on long-term surveillance of biological therapies used in treatment of systemic-onset JIA (260 patients, including 109 treated with tocilizumab) reported higher rates of serious adverse events for tocilizumab (21 per 100 patient years) and canakinumab (20 per 100 patient years) than for anakinra and etanercept (*37*). In particular, cytopenia and hepatic events occurred more frequently with tocilizumab and canakinumab. Rates of macrophage activation syndrome were 2.5 per 100 patient years with tocilizumab,

compared with 3.2 per 100 patient years with canakinumab, 0.83 per 100 patient years with anakinra and 0.05 per 100 patient years with etanercept. Patients treated with tocilizumab and systemic steroids had significantly higher rates of adverse events and serious adverse events than those treated with tocilizumab without systemic steroids: 127.5 per 100 exposure years versus 79.4 per 100 exposure years for adverse events and 28.4 per 100 exposure years versus 15.6 per 100 exposure years for serious adverse events. The adverse events included 93 infectious events in 37 patients on tocilizumab (38 per 100 exposure years; relative risk (RR) 1.40, 95% CI 0.97 to 2.0). Cytopenia was reported in 22 cases, with higher rates in patients on tocilizumab (6.2 per 100 exposure years; RR 5.37, 95% CI 2.19 to 13.17), although these were not significantly higher after adjustment for the presence of systemic signs, and concomitant use of methotrexate and systemic steroids at baseline, and other variables.

Tuberculosis

Patients for whom tocilizumab is considered should be tested for latent tuberculosis before starting the medicine due to a possible risk of tuberculosis reactivation. The American College of Rheumatology recommend that for children at low risk of tuberculosis with a negative initial screening test, testing should be repeated at any point if their risk of tuberculosis changes to moderate–high, as determined by regional infectious diseases guidelines (*22*). Awareness of tuberculosis risk in patients treated with tocilizumab and other biologic DMARD medications is particularly important in low-resource settings with high rates of tuberculosis (*38*).

A systematic review of the literature, which also covered clinical trials and postmarketing surveillance studies, assessed the risk of tuberculosis reactivation in patients with other inflammatory conditions who were receiving biological medicines, including tocilizumab (*39*). Data from clinical trials did not indicate a high risk of tuberculosis reactivation in patients receiving tocilizumab. A small number of cases of tuberculosis have been reported from real-world studies; however, these occurred in countries with a high tuberculosis risk, and they may have been primary tuberculosis infection, rather than reactivation of latent tuberculosis.

Additional evidence (not in the application)

A possible increased risk of reactivation of hepatitis B virus has been reported in patients with rheumatoid arthritis and resolved or chronic hepatitis B virus infection treated with tocilizumab (*40*).

WHO guidelines

WHO guidelines for the treatment of systemic-onset JIA are not currently available.

Costs/cost–effectiveness

A Finnish study that compared the cost–effectiveness of tocilizumab with methotrexate and anakinra using a probabilistic Markov state transition model with a 16-year horizon reported that tocilizumab resulted in 4.47 quality-adjusted life years (QALYs) compared with 3.41 QALYs for methotrexate and 2.83 QALYs for anakinra (*41*). The incremental cost per additional QALY gained for treatment with tocilizumab was € 15 181 compared with methotrexate and € 14 496 compared with anakinra. Based on a willingness-to-pay threshold of € 20 000 per QALY gained, tocilizumab had a 93% probability of being cost–effective compared with methotrexate and 88% compared with anakinra. This probability increased to 100% with a willingness-to-pay threshold of € 27 000 per QALY.

A Canadian cost–effectiveness analysis concluded that tocilizumab with or without methotrexate had an incremental cost–utility ratio of Canadian $ 69 787 per QALY gained compared with placebo with methotrexate and that tocilizumab would be a less costly and more effective treatment from a societal perspective (*42*).

A cost–utility analysis in Thailand assessed the effect of the addition of tocilizumab to standard treatment in patients with refractory systemic-onset JIA (*43*). Using a Markov model with life-time horizon to estimate life-time costs and health outcomes, the incremental cost–effectiveness ratio of standard treatment plus tocilizumab was US$ 35 799 per QALY compared with standard treatment alone.

Availability

Tocilizumab has regulatory approval for the treatment of systemic-onset JIA from many regulatory agencies globally. The intravenous formulation is indicated for children aged 2 years and older, while the subcutaneous formulation is indicated for children aged 1 year and older and weighing at least 10 kg.

The primary patent for tocilizumab has expired and biosimilar products are reportedly in development.

Supply issues and shortages have been reported recently in some countries due to the use of tocilizumab as a novel treatment for COVID-19 and in clinical trials for the treatment of COVID-19.

Other considerations

The availability of a suitably trained workforce to diagnose and treat systemic-onset JIA and manage potential adverse events of treatment is required. Access to specialist paediatric rheumatologists, multidisciplinary teams and treatments is a major challenge in many low-resource countries (*38*). Children treated with tocilizumab (or any biological DMARD) must have access to urgent paediatric rheumatology review and hospitalization if needed, should they develop

complications such as infections. This is particularly important in low-resource countries where up to 50% of deaths in children aged 5–15 years are due to infection (*44*).

Intravenous administration of tocilizumab requires premedication, such as intravenous hydrocortisone and/or an antihistamine, to minimize the risk of an infusion reaction. It has been shown that children who are younger, shorter and lighter and who have high disease activity in the early stages of tocilizumab administration are more likely to experience infusion reactions (*45*).

Committee recommendations

The Expert Committee acknowledged that systemic onset juvenile idiopathic arthritis (JIA) is a subtype of JIA associated with serious morbidity in children, and a higher mortality rate than JIA. The Committee noted that the proportion of children with JIA who have systemic-onset JIA is varies across populations, with lower rates in Europe and higher rates among children in India and Japan.

The Committee acknowledged that management of systemic-onset JIA with disease modifying therapy has the potential to minimize the severe side-effects of corticosteroids and noted that antitumour necrosis factor biological agents were included on the EML and EMLc for juvenile idiopathic arthritis in 2019. The Committee noted that while antitumour necrosis factor biological agents have proven efficacy in many JIA subtypes, they may be less effective for patients with systemic-onset JIA, and anti-interleukin-6 receptor antibodies such as tocilizumab are preferred as the first-line options in some guidance documents. However, the Committee considered that there was uncertainty on the comparative benefit of tocilizumab versus antitumour necrosis factor biological agents because of the low quality of the evidence presented.

The Committee noted that the evidence from the randomized trials presented in the application supported tocilizumab as an effective treatment for systemic-onset JIA. However, the Committee also noted that the evidence all came from trials and studies conducted in well-resourced settings, and that there was uncertainty about the generalizability of findings to lower-resourced settings. Furthermore, local factors (availability of specialist services such as doctors, nurses, urgent review and access to intravenous antibiotics), as well as patient factors (health literacy rates, distance and transport to the hospital, comorbid conditions, poverty and malnutrition) may have significant effects on the rates of adverse events in lower-resource settings.

The Committee noted that tocilizumab is also an expensive medicine, and more expensive than the other disease-modifying medicines included on the EML and EMLc, with potentially important limitations in accessibility and affordability at the country level.

The Expert Committee therefore did not recommend the inclusion of tocilizumab on the EML or EMLc for the treatment of systemic-onset JIA at this

time because of uncertainty in the estimates of clinical benefits, and concerns about limited accessibility and affordability of tocilizumab in different settings.

The Committee acknowledged that treatments for systemic-onset JIA recommended in guidance documents and used in clinical practice include corticosteroids and multiple disease-modifying anti-rheumatic agents, including methotrexate, antitumour necrosis factor biological agents, Janus kinase inhibitors and anti-interleukin-6 receptor antibodies. The Committee requested that a comprehensive evaluation of all medicines used to treat systemic-onset JIA be undertaken for consideration at the next Expert Committee meeting. A comprehensive evaluation of options to treat systemic-onset JIA will support countries to have a better understanding of the additional value and implications of the selection of potential medicines to treat systemic-onset JIA for their national EMLs.

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Triamcinolone – addition – EML and EMLc

Triamcinolone hexacetonide **ATC Code: H02AB08**

Proposal

Addition of triamcinolone hexacetonide on the complementary list of the EML and EMLc for the treatment of juvenile idiopathic arthritis (JIA).

Applicant

Paediatric Global Musculoskeletal Task Force

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

29.3 Juvenile joint diseases

Dose form(s) & strength(s)

Intra-articular injection: 20 mg/mL in 2 mL vial and 20 mg/mL in 10 mL vial

Core/complementary

Complementary

Individual/square box listing

Square box listing with triamcinolone acetonide specified as an alternative.

While it is acknowledged that the available evidence indicates triamcinolone hexacetonide to have greater efficacy, triamcinolone acetonide is proposed as an alternative for use when triamcinolone hexacetonide is not available.

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Triamcinolone hexacetonide has not previously been considered for inclusion on the Model Lists for treatment of JIA.

Acetylsalicylic acid (aspirin) was included in the complementary list of first EMLc in 2007 for JIA (*1*).

In 2019, the Expert Committee considered an application requesting inclusion of antitumour necrosis factor biological agents to the Model Lists for treatment of severe chronic inflammatory autoimmune disorders, including

JIA (*2*). The Committee recognized that autoimmune disorders are highly debilitating and that there is a public health need for effective treatments for patients who do not respond to first-line treatments (e.g. methotrexate). On the basis of the evidence presented and a positive benefit-to-harm profile of the medicines, the Committee recommended the addition of the antitumour necrosis factor antibody adalimumab, with a square box, with therapeutically equivalent alternatives limited to etanercept and infliximab for children (EMLc), and etanercept, infliximab, certolizumab pegol and golimumab for adults (EML). The Committee also recognized that these medicines have a substantial impact on the budget of health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to more market competition.

Public health relevance (burden of disease)

JIA is the most common chronic rheumatic disease of childhood, estimated to affect one in 1000 children (*3*). Worldwide, more than 2 million children are estimated to have JIA, with the greatest prevalence in in Africa and Asia (*4*). JIA is characterized by joint inflammation of more than 6 weeks' duration, with onset before the age of 16 years and absence of another underlying cause (*5*, *6*). It is an autoimmune, inflammatory joint disease, the cause of which remains poorly understood; both genetic and environmental factors are thought to contribute to its development (*7*). The age at onset is typically young, with a peak incidence between 1 and 3 years of age. The disease persists into adulthood in about 50% of cases (*8*).

Even in patients in whom the inflammatory disease resolves, joint or extra-articular damage (such as uveitis) is common. If not treated, JIA can result in irreversible sequelae that substantially affect quality of life (*9*). Uveitis affects up to 30% of children with JIA; if undiagnosed and untreated, this may cause irreversible loss of vision (*10*).

Access to appropriate care is a major problem for many children with JIA (*11*). Given shortages of paediatricians, especially in Asia and Africa, it is likely that many children with JIA have little or no access to specialist care and treatment, resulting in worse clinical outcomes in low-resource settings (*12*, *13*).

The consequences of untreated JIA are known from historical studies that predate current treatment approaches. Essentially, untreated arthritis results in pain, fatigue, joint damage, functional disability and lower quality of life. It is likely that the burden of untreated JIA is high, especially in low-resource settings where the true burden is probably under-recognized (*14*, *15*).

The early introduction of disease modifying therapy is now the standard of care in high-resource settings (*16*, *17*).

Summary of evidence: benefits (from the application)

Intra-articular corticosteroids are recommended in treatment guidelines as first-line therapy for oligoarticular forms of JIA (*18–20*). Triamcinolone hexacetonide and triamcinolone acetonide are the two most commonly used long-acting steroids for JIA treatment. The application summarized the results of clinical studies as evidence for the benefit of triamcinolone hexacetonide and triamcinolone acetonide in the treatment of JIA.

Note: the terms pauciarticular juvenile rheumatoid arthritis or juvenile chronic arthritis, which are used below because they are found in some of the old studies cited, are equivalent to oligoarticular JIA.

A prospective study evaluated the effect of steroid injections in 40 children with pauciarticular juvenile rheumatoid arthritis and other oligoarticular forms of inflammatory arthritis who had failed therapy with non-steroidal anti-inflammatory drugs (*21*). Active joints were injected with 20–40 mg of triamcinolone hexacetonide. In 50% of the joints of children with juvenile rheumatoid arthritis and 30% of children with other forms of inflammatory arthritis, a good response, defined as complete resolution (by clinical examination) of active joint inflammation, was maintained for 12 months. No statistically significant differences were found according to disease group, sex or administered dose.

A retrospective study of 194 children with all juvenile chronic arthritis subgroups reviewed treatment with either single or repeated triamcinolone hexacetonide injections (*22*). Efficacy and duration of benefits were evaluated after a mean duration of 3, 15, 30 and 64 weeks. Responses differed significantly among subgroups ($P = 0.0001$): efficacy of treatment lasted for 121 weeks in early-onset pauciarticular juvenile chronic arthritis type I, for 47 weeks in late-onset pauciarticular juvenile chronic arthritis type II and for 105 weeks in rheumatoid-factor negative polyarticular juvenile chronic arthritis. The study concluded that intra-articular triamcinolone hexacetonide was an effective therapy for all subgroups of juvenile chronic arthritis inflammatory joint disease.

An open-label, non-randomized, prospective study compared the efficacy and safety of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in 85 patients (130 joints) with JIA (*23*). The response, defined as the absence of inflammation or a decrease in joint inflammation leading to a reduction in the articular score of > 60% from baseline, was significantly higher with triamcinolone hexacetonide than with triamcinolone acetonide: 81.4% versus 53.3%, P = 0.001 at 6 months; 67.1% versus 43.3% at 12 months, $P = 0.006$; and 60.0% versus 33.3%, $P = 0.002$ at 24 months). The rate of relapse, defined as the reappearance of arthritis after a period of good response, was 2.7 times greater in the triamcinolone

hexacetonide group (95% confidence interval (CI) 1.6 to 4.8). The time to relapse for triamcinolone hexacetonide and triamcinolone acetonide was compared in a retrospective study of 85 patients with JIA (227 joints) (*24*). After adjusting for sex, duration of illness or type of arthritis, triamcinolone hexacetonide was associated with a significantly longer time to relapse.

A double-blind trial compared the outcomes in 37 children with JIA (86 joints) who received an intra-articular injection of triamcinolone hexacetonide (up to 1 mg/kg per joint) or triamcinolone acetonide (up to 2 mg/kg per joint) in symmetrical joints (*25*). All joints improved after injection; however, after between 2 and 21 months of follow up, 21 (53.8%) joints injected with triamcinolone acetonide relapsed compared with six (15.4%) joints in the children who received triamcinolone hexacetonide. The rate of persisting or sustained response was higher with triamcinolone hexacetonide than with triamcinolone acetonide (89.7% versus 61.5%, $P = 0.008$ at 6 months; 84.6% versus 48.7%, $P = 0.001$ at 12 months; and 76.9% versus 38.5%, $P = 0.001$ at 24 months).

Summary of evidence: harms (from the application)

The adverse event profiles of triamcinolone hexacetonide and triamcinolone acetonide are similar (*6*, *16*, *23*, *25*, *26*) and include: infection (septic arthritis at the injection site); subcutaneous atrophy caused by extravasation of the drug from the joint space; steroid lipodystrophy; postinjection pain; calcium deposition in the joint; systemic absorption; and avascular necrosis of the hip joint. Most adverse events can be reduced with good clinical technique and accurate needle placement; hence the recommendations that joint injections be performed by appropriately trained clinicians (*16*, *17*).

A study on the safety of intra-articular triamcinolone hexacetonide for the treatment of coxitis in patients with JIA reported a prevalence of avascular necrosis of the femoral head of the hip joint of 2.4 cases per 100 patient years in children receiving both intra-articular and systemic corticosteroid treatment (*27*). Avascular necrosis of the hip was not observed in children who received only intra-articular corticosteroids.

The use of triamcinolone is contraindicated if any of the following are present: active tuberculosis, systemic mycoses, parasitoses, Herpes simplex keratitis and acute psychoses (due to the potential effect of the systemic absorption of steroids).

Additional evidence (not in the application)

Not applicable

WHO guidelines

WHO guidelines for the management of juvenile idiopathic arthritis are not currently available.

Costs/cost–effectiveness

The cost per vial of triamcinolone (hexacetonide or acetonide) varies across countries.

The cost of treatment per child depends on the number of joints to be injected and the size of each joint. The cost of treatment per patient is therefore highly variable and may differ depending on the cost of the medicines and which agent is used.

Triamcinolone hexacetonide has been found to be more effective and give a more sustained response compared with comparable doses of triamcinolone acetonide (*23*). Therefore, the application concluded that triamcinolone hexacetonide may be more cost-effective. However, no formal studies of the overall cost–effectiveness of intra-articular steroids in JIA were available.

The cost of untreated JIA is likely to be very high for patients, their families and society (*28*).

Availability

Shortages of triamcinolone hexacetonide are reported around the world.

In 2020, the Aristospan® brand of triamcinolone hexacetonide was listed as short in supply in the United States of America and has been discontinued on the US market by the Food and Drug Administration; however, it can be imported on an individual patient basis. Triamcinolone hexacetonide is not approved for use in Australia by the Therapeutic Goods Administration but can be accessed through the Special Access Scheme from international manufacturers. Canada recently approved triamcinolone hexacetonide for inclusion in their public drug formularies. Triamcinolone hexacetonide has marketing approval for intra-articular use in the United Kingdom and is included in the British National Formulary.

Triamcinolone acetonide has regulatory approval for intra-articular administration in Australia, New Zealand and the USA. It has marketing authorization in Canada, Sweden and Switzerland.

Other considerations

Joint injections are uncomfortable and analgesia with local, inhaled or general anaesthesia or sedation is recommended, especially if several joints are injected.

Imaging (such as ultrasound or radiographic image intensifier) can be used to optimize the accuracy of needle placement – especially for small joints or deep joints such as the hip or subtalar joints (*16*, *29*).

It is recommended that triamcinolone be administered only by appropriately trained clinical personnel, experienced in using intra-articular steroids to treat active joint disease in JIA (*6*, *16–19*, *30*).

Committee recommendations

The Expert Committee noted that juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and is associated with significant morbidity, functional disability and reduced quality of life.

The Committee noted that the evidence presented supporting the use of intra-articular corticosteroids in JIA was limited and sub-optimal quality. Almost all studies were in high-income countries and specialized settings and the generalizability of findings to lower-resourced settings is uncertain. No data were included on the role and the comparative benefits and risks of triamcinolone hexacetonide compared with oral corticosteroids or disease modifying treatments such as methotrexate. Although, intra-articular steroids are considered an important tool in the treatment of JIA, the Committee noted that consensus is lacking about their efficacy and safety in different settings. The lack of consensus was also reflected in the discussion of the application during the meeting.

The Committee noted that administration of intra-articular corticosteroids for both adults and children is an invasive procedure associated with risks (such as infection) and requires specialized training and experience. Adjusting the corticosteroid dose based on the targeted anatomical joint is an important aspect of practice, as overdose of corticosteroids might lead to joint atrophy. Laboratory tests are needed to determine disease activity and risk of progression, and to evaluate a patient's suitability for treatment with intra-articular corticosteroid injections. The Committee also expressed concerns about the limited availability of specialist paediatric rheumatology care in low- and middle-income settings.

The Expert Committee therefore did not recommend the inclusion of triamcinolone hexacetonide on the EML or the EMLc at this time, because of the uncertain clinical benefit of triamcinolone hexacetonide given the low quality of evidence and its limited generalizability, and safety concerns associated with administration procedures.

However, recognizing the need for effective and safe treatments for JIA, the Committee requested that a comprehensive evaluation of all medicines used in the treatment of JIA be undertaken for consideration at the next Expert Committee meeting.

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Section 30: DENTAL PREPARATIONS

Fluoride toothpaste – addition – EML and EMLc

Fluoride toothpaste — ATC Code: A01AA

Proposal

Addition of fluoride toothpaste on the core list of the EML and EMLc for the prevention of dental caries.

The application also proposed the transfer of the current listing for sodium fluoride to a new section of the Model Lists for dental preparations.

Applicant

Benoit Varenne; WHO Oral Health Programme

WHO technical department

Noncommunicable Diseases

EML/EMLc

EML and EMLc

Section

30. Dental preparations

Dose form(s) & strength(s)

Fluoride toothpaste: paste, cream or gel containing between 1000 and 1500 parts per million (ppm) fluoride (any type)

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Sodium fluoride tablets were first included on the EML in 1979 for use as a prophylactic measure against dental caries where water supplies are not fluoridated (*1*).

In 1993, the listing was amended to accommodate other formulations. In 2005, a proposal to remove sodium fluoride was considered by the Expert Committee. In consideration of this proposal, the Committee noted that the

efficacy of topical fluoride preparations in preventing dental caries was firmly established. The Committee also noted that the selection of a suitable fluoride preparation should take into account local circumstances, including the fluoride content of drinking-water. Fluoride tablets are no longer recommended because of the risk of fluorosis when they are used in excess. The Committee therefore recommended that sodium fluoride be retained on the Model List, but that the description be changed to "in any appropriate topical formulation" (*2*). In 2007, sodium fluoride was included in the first edition of the EMLc (*3*).

Public health relevance (burden of disease)

The 2017 Global Burden of Disease Study estimated that oral diseases affect close to 3.5 billion people worldwide, with caries of permanent teeth being the most common condition. Globally, 2.3 billion people are estimated to suffer from caries of permanent teeth and more than 530 million children suffer from caries of primary teeth (*4*). Most caries are untreated. The caries burden is very unequal across populations within and between countries, with a clear socioeconomic gradient showing higher disease burden in deprived and disadvantaged populations who at the same time have less access to care, including preventive care (*5*). Caries is a disease of all age groups with an onset in early childhood and continued increase over the life course. Most significant increases in incidence are observed in adolescent age groups.

A high prevalence and severity of untreated dental caries is associated with low body mass index and stunting; it also leads to considerable absenteeism in school and the workplace.

The use of fluoride toothpaste is a public health intervention designed for self-care as part of daily toothbrushing for all age groups throughout the life course. Assessment of current use is challenging as it is dependent on personal oral hygiene habits and affordability/availability of fluoride toothpaste to the individual.

Use of fluoride toothpaste has been assessed in some populations and sub-groups using self-reported surveys which tend to over-report. Reported rates of toothbrushing with fluoride toothpaste vary: about 60% of children in the United States of America (*6*), 70% of all age groups in Portugal (*7*), 50% of children in Lithuania and 80% of children in Sweden (*8*). Similar rates are reported from the global school-based health survey (*9*, *10*). In Burkina Faso, only 9% of 12-year-old children and 18% of 35–44-year-old adults reported use of fluoride toothpaste (*11*), and in rural China only 2% of children use fluoride toothpaste (*12*). Most of these studies only report toothbrushing behaviour and do not specifically ask about the use of fluoride toothpaste. Reliable data on use of fluoride toothpaste in adults are not available. In the absence of publicly available sales information from manufacturers, the global use of fluoride toothpaste has been estimated at around 1.5 billion people (*13*).

The low affordability of fluoride toothpaste is a significant obstacle to its use, particularly for poor populations in low- and middle-income countries (*14*). WHO conducted a survey on affordability of fluoride toothpaste for an upcoming WHO global oral health report, analysing data from 80 countries and using the WHO/Health Action International methodology. The survey documented a large variation in prices of fluoride toothpaste and high costs, particularly for the poorest 15% of the population in countries of sub-Saharan Africa, parts of south and south-east Asia and the Pacific Islands. In these countries, the cost of an annual supply of fluoride toothpaste per person would lead to catastrophic health expenditure.

Globally, the prevalence and incidence of untreated caries changed little between 1990 and 2017 (*4*), while the total number of individuals affected significantly increased due to population demographics, particularly in low- and middle-income countries. At the same time high-income countries observed a strong and consistent decrease in the caries burden, which coincided with the introduction of fluoride toothpaste to markets in the early 1960s (*15*). Increased use and affordability of fluoride toothpastes are expected to have similar effect on current populations in low- and middle-income countries (*16*). WHO global and regional policy documents and implementation manuals emphasize the importance of fluoride toothpaste and prioritize measures to improve quality, accessibility and affordability (*17–20*).

Summary of evidence: benefits (from the application)

The application presented a summary of available Cochrane and other systematic reviews as evidence for the effectiveness of fluoride toothpaste in children, including in prevention of early childhood caries, and adults.

A 2019 Cochrane review of 94 studies published between 1955 and 2014 evaluated the effects of toothpastes of different fluoride concentrations (between 1000 ppm and 2800 ppm) in preventing dental caries in children, adolescents and adults (*21*). The review findings supported the benefits of using fluoride toothpaste for the prevention of caries compared with non-fluoride toothpaste. For fluoride concentration, a dose–response effect was observed in children and adolescents. In adults, a fluoride concentration of 1000 ppm or 1100 ppm was found to reduce caries compared with non-fluoride toothpaste.

A 2003 Cochrane review and meta-analysis of 70 studies (42 300 participants) evaluated the effectiveness and safety of fluoride toothpastes in the prevention of dental caries in children. The main outcome of the studies was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS) (*22*). The preventive fraction (the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group) in the permanent dentition using

a 1500 ppm fluoride toothpaste was 24% (95% confidence interval (CI) 21 to 28%; $P < 0.0001$). For a population with a caries increment of 2.6 D(M)FS per year, 1.6 children would need to brush with a fluoride toothpaste over 3 years to prevent one D(M)FS. The effect of fluoride toothpaste increased with higher baseline caries levels, higher fluoride concentration, higher frequency of use and supervised toothbrushing.

A 2004 Cochrane review of 12 studies compared the effectiveness of two topical fluoride treatments (e.g. toothpastes, mouth rinses, gels and varnishes) used together with one of the treatments alone (mainly toothpaste) when used for the prevention of dental caries in children (*23*). Compared to mouth rinses and gels, fluoride toothpastes had similar effectiveness for the prevention of dental caries in children.

A systematic review and meta-analysis of eight clinical trials evaluated the effects of fluoride toothpastes on the prevention of dental caries in the primary dentition of preschool children (*24*). A significant reduction in caries was observed at surface, tooth and individual levels for standard fluoride toothpastes (1000–1500 ppm) compared with placebo or no intervention. The authors concluded that the use of standard fluoride toothpastes should be recommended for use by preschool children.

Summary of evidence: harms (from the application)

The harms and toxicity of fluoride toothpaste have been analysed by several high-quality Cochrane and other systematic reviews (*21*, *22*, *25*, *26*). A recent WHO report reviewed the state of the evidence (*27*). In summary, the harms and toxicity of fluoride toothpaste are related to either toxicity through ingestion (unintentional/intentional) and to the risk of dental fluorosis (the hypomineralization of the enamel caused by ingestion of excessive fluoride levels during tooth formation).

The risk of acute fluoride toxicity occurs when young children ingest large amounts of toothpaste. There are no reports in the literature of such events. The US Food and Drug Administration stipulates that the total amount of fluoride in any package sold over the counter must not be more than 276 mg to prevent problems if the whole tube is swallowed. For the same reasons, the International Organization for Standardization standard ISO11609 limits the maximum fluoride content of a single-size container to 300 mg unless a larger container is used in a supervised community context and not sold over the counter (*28*).

While the main sources of ingested fluoride are water from areas with high concentrations of natural fluoride, food or certain teas, there is a risk of dental fluorosis from the ingestion of toothpaste by young children during tooth development (either of the deciduous or permanent teeth) (*26*).

Use of a pea-size amount of fluoride toothpaste was not associated with mild to moderate fluorosis and the concentration of fluoride in toothpaste was also not associated with fluorosis risk (*15*, *26*, *27*).

Other side-effects of fluoride toothpaste have not been reported apart from reactions to other ingredients of toothpaste formulations (e.g. surfactants).

Measures to reduce the risk of fluorosis include recommendations and package labelling requesting supervision of children while brushing, limiting the amount of toothpaste used and the limitation of total fluoride content in a single toothpaste container (*27*, *28*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

The 1994 WHO technical report on fluorides and oral health details evidence for various delivery forms of fluorides, their dosage, risks, side-effects and monitoring (*29*). Since then, the evidence has been complemented by evolving science and consensus as documented in other WHO and WHO-led documents (*27*, *30*, *31*), Cochrane systematic reviews (*21*, *22*, *25*), and recommendations and clinical guidelines from the US Centers for Disease Control and Prevention and other major public health and professional organizations (*32*–*35*).

Their recommendations are summarized below.

- Toothpaste should contain at least 1000 ppm of fluoride (w/w 1000 mg fluoride/kg = 1 mg fluoride/g) and no more than 1500 ppm of fluoride.
- Special formulations for children are not recommended due to lack of evidence that toothpaste containing less than 1000 ppm fluoride prevents caries.
- For children younger than 3 years, begin brushing as soon as teeth erupt using no more than a smear of fluoride toothpaste the size of a rice grain of regular (adult) toothpaste. Parents/caregivers should brush children's teeth twice a day or as directed by a dentist or physician. Supervision is required to ensure that toothpaste slurry is not swallowed but spat out without subsequent rinsing.
- Children 3–6 years should brush teeth with a pea-sized amount of regular (adult) toothpaste. Parents/caregivers should brush children's teeth twice a day or as directed by a dentist or physician. Supervision is required to ensure that toothpaste slurry is not swallowed but spat out without subsequent rinsing.

- Children older than 6 years, adolescents and adults should brush teeth twice a day with a pea-sized amount of fluoride toothpaste without subsequent rinsing.

Costs/cost–effectiveness

As a personal preventive and hygiene activity, the cost of fluoride toothpaste and toothbrushes is an out-of-pocket expense, apart from limited community programmes for children where toothpaste cost is otherwise covered. Prices of toothpaste vary considerably between available brands, fluoride compounds and package sizes, as well as between countries. In a number of countries, taxes and import duties are markedly increasing consumer cost, leading to considerations around manufacturing an affordably priced toothpaste for low- and middle-income countries (*14*, *36*, *37*).

Fluoride toothpaste is considered to be cost-effective, with costs per usage (one toothbrushing event) of less than US$ 0.05 or annual supply per person between US$ 0.50 and US$ 36.50 (*38*, *39*). All school-based oral health programmes include some form of supervised or unsupervised toothbrushing with fluoride toothpaste. Several studies have demonstrated the high cost–effectiveness of such an approach (*36*, *40*, *41*).

The cost–effectiveness of fluoride toothpaste is still higher than other fluoride interventions, although there is no other intervention that combines cleaning of teeth and gums with caries-preventive measures. Toothbrushing without fluoride toothpaste has no caries-preventive effect (*38*).

Availability

Fluoride toothpaste is available worldwide. In most countries, it is regulated as a cosmetic product (or medical device or medicinal product) for products containing up to 1500 ppm fluoride. Toothpastes with a higher fluoride concentration (up to 5000 ppm fluoride) are often regulated as medicines or medical products requiring a prescription.

Other considerations

European Union regulation (*42*) specifies labelling for dosage and strengths of 21 different fluoride compounds in fluoride toothpaste: nicomethanol hydrofluoride, magnesium fluoride, ammonium monofluorophosphate, sodium monofluorophosphate, potassium monofluorophosphate, calcium monofluorophosphate, sodium fluoride, potassium fluoride, ammonium fluoride, aluminium fluoride, stannous fluoride, cetylamine hydrofluoride, 3(N-hexadecyl-N-2-hydroxyethylammonio)propylbis(2-hydroxyethyl) ammonium difluoride, N,N′,N′-tris(polyoxyethylene)-N-hexadecylproyplenediamine dihydrofluoride, octadecenyl-ammonium fluoride, sodium fluorosilicate, potassium fluorosilicate, ammonium fluorosilicate, magnesium fluorosilicate, nicomethanol hydrofluoride

and magnesium fluoride. The active ingredient must be listed. In addition, "For any toothpaste with compounds containing fluoride in a concentration of 0.1 to 0.15% calculated as F unless it is already labelled as contra-indicated for children (e.g. 'for adult use only') the following labelling is obligatory: 'Children of 6 years and younger use a pea-sized amount for supervised brushing to minimize swallowing. In case of intake of fluoride from other sources consult a dentist or doctor.'"

In the USA, all anticaries fluoride drug products for over-the-counter human use are regulated by the US Food and Drug Administration under Code of Federal Regulations Title 21 (*43*). The accepted active ingredients are:

- Sodium fluoride. Dentifrices containing 850–1150 ppm of theoretical total fluorine in the formulation.
- Sodium monofluorophosphate. Dentifrices containing 850–1150 ppm and 1500 ppm of theoretical total fluorine.
- Stannous fluoride. Dentifrices containing 850–1150 ppm of theoretical total fluorine.

To avoid acute toxicity from ingestion, packages should not contain more than 276 mg of total fluoride. There are restrictions on labelling and warnings about direct ingestion. Lower fluoride formulations are not authorized for use in the USA but are sold in other parts of the world, despite a lack of evidence that they prevent caries.

Committee recommendations

The Expert Committee noted that dental caries of permanent teeth affects an estimated 2.3 billion people worldwide and more than 530 million children suffer from caries of primary teeth. Inequalities throughout the life course and across populations in the low-, middle- and high-income countries were also noted, with the highest burden in countries with limited resources for caries prevention and control.

The Expert Committee noted that the use of fluoride toothpaste reduces caries lesions by one quarter compared with non-fluoride toothpaste, according to cumulative data across studies.

Despite fluoride toothpaste being a foundation of oral health prevention strategies, the Committee observed that the current listing for sodium fluoride in the EML and EMLc does not specify the form and concentration range of topical fluoride products used to prevent dental caries, specifying only "in any appropriate topical formulation". The Committee considered that to provide the best guidance for selection of products for national EMLs, the Model Lists should include specific recommendations of the different formulation types and ideal concentrations of fluoride-containing preparations.

The Expert Committee took into account that fluoridated toothpaste containing between 1000 ppm and 1500 ppm fluoride is the standard strength recommended by WHO as a public oral health measure to prevent caries. The Committee also considered that to prevent the risk associated with ingestion of toothpaste, limitation of package size and maximum fluoride content for a single unit with a well defined concentration range would be helpful. Furthermore, the Committee noted the risk of substandard toothpastes being marketed with low or nil concentration of fluoride. Specifying fluoride amount and concentration can help national authorities to develop standards for production and to implement quality-control actions to identify marketed toothpastes that do not meet recommended fluoride standards. The Committee also noted that additional fluoride sources (e.g. water supply) should be taken into consideration by countries.

The Expert Committee recommended that the current listing for sodium fluoride be transferred from Section 27 (Vitamins and Minerals) to a new section of the EML and EMLc for dental preparations. The listing should be amended to "fluoride", noting that topical fluoride-containing preparations use fluoride in a variety of forms. Fluoride toothpaste is recommended for inclusion as a specifically defined formulation of fluoride (paste, cream or gel containing between 1000 ppm and 1500 ppm fluoride any type), because of its proven effectiveness in preventing dental caries and for better control of the quantity of fluoride contained in toothpaste. The Committee requested WHO to identify and define the alternative fluoride-containing formulations that are recommended for use in the prevention of dental caries so that these can be clearly indicated in the Model Lists in 2023 to provide clear guidance to countries.

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Glass ionomer cement – addition – EML and EMLc

Glass ionomer cement **ATC Code: N/A**

Proposal

Addition of glass ionomer cement on the core list of the EML and EMLc for the prevention and treatment of dental caries in adults and children.

Applicant

Benoit Varenne; WHO Oral Health Programme

WHO technical department

Noncommunicable Diseases

EML/EMLc

EML and EMLc

Section

30. Dental preparations

Dose form(s) & strength(s)

Single-use capsules: 0.4 g powder + 0.09 mL liquid

Multiuse bottle: powder + liquid

Powder (fluoroaluminosilicate glass) contains: 25–50% silicate, 20–40% aluminium oxide, 1–20% fluoride, 15–40% metal oxide, 0–15% phosphate, and polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7–25% polybasic carboxylic acid and 45–60% polyacrylic acid.

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Glass ionomer cement has not previously been considered for inclusion on the Model Lists.

Preventing caries with dental sealant

Clinical application of glass ionomer cement as a dental sealant can be performed as a preventive intervention without any caries present. The procedure can be

carried out in a dental clinic or in a community setting such as in a school. The therapeutic effect does not require long-term retention of the bulk material, so monitoring is not essential. Minimal training for a dental assistant, dental therapist, dental nurse, dental hygienist or dentist is required, but non-dental health care workers have also been successfully trained to apply dental sealants.

Glass ionomer cement should be applied early after eruption of both primary and permanent molars. Treatment is done once per erupting molar tooth; for example, sealing four permanent first molars at around 6 years and sealing four permanent second molars at around 12 years.

Treating carious lesions with a filling

Glass ionomer cement can be used to fill cavities using the atraumatic restorative treatment procedure and is endorsed by WHO for caries management across the life course (*1*, *2*).

Public health relevance (burden of disease)

The 2017 Global Burden of Disease Study estimated that oral diseases affect close to 3.5 billion people worldwide, with caries of permanent teeth being the most common condition. Globally, 2.3 billion people are estimated to suffer from caries of permanent teeth and more than 530 million children suffer from caries of primary teeth (*3*). Most caries are untreated. The caries burden is very unequal across populations within and between countries, with a clear socioeconomic gradient showing higher disease burden in deprived and disadvantaged populations who at the same time have less access to care, including preventive care (*4*). Caries is a disease of all age groups with an onset in early childhood and continued increase over the life course. Most significant increases in incidence are observed in adolescent age groups.

A high prevalence and severity of untreated dental caries is associated with low body mass index and stunting; it also leads to considerable absenteeism in school and the workplace. Good oral health is also vital for healthy ageing, playing a crucial role with regard to nutrition.

Globally, prevalence and incidence of untreated caries changed little between 1990 and 2017 (*3*), while the total number of individuals affected significantly increased due to population demographics, particularly in low- and middle-income countries. As most tooth decay is untreated, all forms of prevention are essential, including fluoride toothpaste and other forms of fluoride delivery, and dental sealants. After the onset of the carious process and cavitation, simple, cost-effective options for dental fillings need to be available to improve access and affordability of restorative dental care, and to avoid tooth extraction as the only other treatment option.

The Minamata Convention on Mercury requests a phase-down of dental amalgam, the current most commonly used dental filling material, due to its

mercury content (*5*, *6*). In view of the burden of untreated caries and the need to expand coverage of basic dental services in the context of universal health coverage, the availability of glass ionomer cement as an alternative dental filling material is very important (*5*, *7*). Moreover, glass ionomer cement is one of the public health tools to provide appropriate levels of fluoride for dental health and to address early childhood caries (*1*, *8*, *9*).

Glass ionomer cement is a dental material with widespread global use for treatment and prevention of dental caries. It has caries-preventive properties due to continued capture and release of fluoride ions that remineralize carious tooth structures and have a bacteriostatic effect. Glass ionomer cement results in lower rates of recurring caries compared with composite resin or amalgam fillings; its use also reduces the incidence of new cavities in other teeth. The simplicity of application makes glass ionomer cement suitable in primary health care and field settings, as it does not require specialized equipment including curing lights. Furthermore, since the application of glass ionomer cement does not require extensive dental training, it can be used to provide people living in rural and remote areas and otherwise disadvantaged populations with access to dental care for caries through the primary health care system (*4*).The hydrophilic nature of glass ionomer cement makes application in the field much easier where moisture control is a problem.

The expected health-related positive effects of glass ionomer cement sealants and fillings include: improved quality of life through reduction of pain and infection from caries, reduced absence from school and work and substantial cost savings for health systems.

Summary of evidence: benefits (from the application)

The summary of evidence presented in the application was minimal.

A review of the cited references was conducted by the EML Secretariat and a summary is provided below.

A 2017 Cochrane systematic review of 38 trials (7924 participants) evaluated the effects of different types of fissure sealants in preventing caries in permanent teeth in children and adolescents (*10*). Within this review, three trials (905 participants) evaluated glass ionomer sealant versus no sealant and found inconclusive results. Two of the studies slightly favoured glass ionomers compared with no sealant (*11*, *12*), while the third found no significant difference between sealant and no sealant (*13*). The authors concluded that there was insufficient evidence to judge the effectiveness of glass ionomer sealants. However, the review found that resin-based sealants reduced caries by between 11 and 51 percentage points compared with no sealant at 24 months (*10*).

A 2008 meta-analysis of six studies evaluated the effectiveness of dental sealants in preventing the progression of caries lesions in pits and fissures of

permanent teeth (*14*). Four studies used resin-based sealants and two used glass ionomer cement. For the individual studies combined, the median prevented fraction was 74.2% (range 61.6–100.0%). In the two glass ionomer cement studies, the median prevented fraction was 86.5% (range 73–100%). Overall, the median prevented fraction did not vary greatly by sealant type and always exceeded 60%. The authors concluded that the sealing of caries lesions reduces the probability of lesion progression. Because non-cavitated lesions accounted for almost 90% of teeth in this meta-analysis, the evidence supporting the sealing of non-cavitated lesions was stronger than that for the sealing of cavitated lesions.

A 2003 review of evidence for the use of pit and fissure sealants in preventing caries in the permanent dentition of children found that retention rates for glass ionomer cements (continued adherence of the sealant to the tooth) were lower than that of resin-based sealants, and the authors did not recommend their use (*15*).

Guidelines developed by the American Dental Association and the American Academy of Pediatric Dentistry included a meta-analysis of 10 randomized controlled trials comparing glass ionomer sealants with resin-based sealants. The analysis found that use of glass ionomer sealants may reduce the incidence of occlusal carious lesions in permanent molars by 37% after 2 to 3 years of follow-up (odds ratio (OR) 0.71, 95% confidence interval (CI) 0.32 to 1.57) however, this difference was not statistically significant. In absolute terms, for a population with a caries baseline risk of 30%, use of a glass ionomer sealant would prevent 67 carious lesions out of 1000 sealant applications (95% CI 102 more to 179 fewer). In patients with non-cavitated occlusal carious lesions, glass ionomer sealants may increase the incidence of carious lesions by 53% (OR 1.53, 95% CI 0.58 to 4.07). Glass ionomer sealants were found to have a five times greater risk of loss of retention from the tooth compared with resin-based sealants (OR 5.06, 95% CI 1.81 to 14.13). The guideline panel determined the overall quality of the evidence for this comparison as very low owing to a serious risk of bias (unclear method for randomization and allocation concealment), inconsistency and imprecision (*16*).

A systematic review of six trials evaluated the caries-preventive effect of high-viscosity glass ionomer and resin-based fissure sealants on permanent teeth (*17*). No statistically significant differences were found between treatments at 48 months (risk ratio (RR) 0.62, 95% CI 0.31 to 1.21) but a borderline significant difference in favour of high-viscosity glass ionomer sealants was seen after 60 months (RR 0.29, 95% CI 0.09 to 0.95). However, the authors of the review noted that the included trials had a high risk of bias.

A randomized trial evaluated the effect of fluoride-releasing sealants on adjacent tooth surfaces in children aged 6–7 years (*18*). High-viscosity glass ionomer cement and resin-based sealants with fluoride were shown to protect against dental caries, with evidence that these materials also reduced the incidence of new caries on untreated teeth adjacent to the sealed tooth.

A 2018 systematic review and meta-analysis evaluated the survival percentages of dental restorations of high-viscosity glass ionomer cement fillings placed in permanent teeth using an atraumatic restorative technique (*19*). Over the first 2 years, the survival percentages of single- and multiple-surface atraumatic restorative treatment restorations in primary posterior teeth were 94.3% and 65.4%, respectively. Over the first 3 years, the survival percentage for single-surface restorations was 87.1%. For multiple-surface restorations, the survival percentage over the first 5 years was 77%.

A systematic review of 38 trials including over 10 000 tooth restorations found no statistically significant differences in failure rates between high-viscosity glass ionomer cement and amalgam restorations in single- and multiple-surface tooth cavities up to 6 years. However the trials had a high risk of bias due to inadequate randomization and allocation concealment, and a high risk of performance, detection and attrition bias (*20*).

Findings from an indirect treatment comparison of failure rates between high-viscosity glass ionomer cement and composite resin restorations in posterior permanent teeth found no statistically significant difference between restoration types (*21*). However, the limitations of the indirect comparison and the lack of direct comparative data were noted.

Summary of evidence: harms (from the application)

A recent Cochrane systematic review of pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents included five trials that reported adverse events – four using resin-based sealants and one using resin-modified glass ionomer (*22*). No adverse effects were associated with the use of either sealant type or fluoride varnishes.

Various in vitro and in vivo studies of glass ionomer and resin sealants did not find any significant negative effects on pulp, dentine or gingival tissues and cells (*23*, *24*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

The WHO implementation manual on ending childhood dental caries (*2*) states the following in relation to glass ionomer cement.

- Placement of pit- and-fissure sealants in molar teeth can reduce the development and progression of new carious lesions into dentine. Different types of sealant material have their own merits, but glass ionomer sealants, which are less demanding on technique and moisture control, are often suitable for use in young children and in community settings.
- If restoration of decayed primary teeth is required, preference should be given to the use of minimally invasive techniques such as atraumatic restorative treatment using adhesive materials such as glass ionomer cement, especially when provided in community settings. These techniques do not require a local anaesthetic injection and, being less invasive, are more "child-friendly". Survival of single surface atraumatic restorative treatment restorations using high-viscosity glass-ionomer in primary teeth is high and can be comparable to that of restoration placed using a conventional approach.

Costs/cost–effectiveness

The average costs of dental sealant, atraumatic restorative treatment or conventional filling using glass ionomer cement are between US$ 2 and US$ 3 per application on multiple teeth (*10*, *25*, *26*). Average conventional fillings using other materials cost between € 8 and € 156 in Europe. However, comparability of data is limited and depends on the size and location of the filling and additional supplies or procedures included in the costing (*27*).

A cost–benefit study in China assessed the incremental cost of four different glass ionomer cement sealant types in preventing one cavity in permanent molars of schoolchildren. Costs ranged between US$ 52 and US$ 105 per 1000 sealants (*28*). The authors concluded that "ease of application, minimal technical and infrastructure requirements, and cost–effectiveness make glass ionomers a practicable option for governments making decisions under economic constraints".

Availability

The application considered that it was safe to assume that glass ionomer cement was available worldwide and regulated as a medicinal product.

Other considerations

Aspects of glass ionomer cement are standardized by the International Organization for Standardization (ISO) under standard ISO 9917-1:2007, such as testing methodology, minimum requirements, labelling and other matters (*29*).

In the European Union, glass ionomer cement must conform to European Union Council Directive 93/42/EEC concerning medical devices and falls under Class IIa (*30*).

Committee recommendations

The Expert Committee noted that dental caries of permanent teeth affects 2.3 billion people worldwide and more than 530 million children suffer from caries of primary teeth. Inequalities throughout the life course and across populations in low-, middle- and high-income countries were also noted, with the highest burden in countries with limited resources for prevention and control. In those settings, primary oral health care is often limited by a lack of essential supplies such as filling material, leading to an unnecessary focus of treatment on tooth extraction, even when a tooth-saving filling would still be an option.

The Expert Committee also considered Resolution EB148/1 of the WHO Executive Board adopted in January 2021, in which Member States requested WHO to develop technical guidance on environmentally friendly and less invasive dentistry to support countries with their implementation of the Minamata Convention on Mercury, including supporting preventative programmes.

The Committee noted that high-viscosity glass isomer cement has caries-preventive properties due to continued capture and release of fluoride ions that remineralize carious tooth structures and have a bacteriostatic effect. In addition, glass isomer cement results in lower rates of recurring caries compared with composite resin or amalgam fillings, and reduces the incidence of new cavities in other teeth.

The Expert Committee took into consideration that dental sealants, including glass ionomer cement, have been shown to be highly effective in preventing dental caries. The main advantage of glass ionomer cement over other sealants is the simplicity of application. This makes glass ionomer cement suitable for use in atraumatic restorative treatment for dental caries by dentists and other health professionals in primary health care, and community and field settings outside of specialized dental clinics. The Committee noted that while other types of sealants or fillings (e.g. resin-based products) are at least equally as effective as glass ionomer cement sealants and potentially have better mechanical properties (e.g. adherence to the tooth), they require more specialized expertise and application techniques and conditions (e.g. need for electricity). Glass ionomer cement is particularly suitable for people who are unable to tolerate conventional invasive dental treatment, such as young children, elderly people and patients with mental health conditions who may have difficulty cooperating. In certain conditions, glass ionomer cements are indicated for everyone. From the mechanical and optical perspectives in dentistry, better material alternatives are available, namely resin composites or ceramics. However, these alternatives are sensitive to the application technique and are costly compared with glass ionomer cements.

The Expert Committee, therefore, recommended including glass ionomer cement in the core list of the EML and EMLc in the new section for dental preparations on the basis of its relevant benefits in the prevention of dental caries and its advantages in atraumatic restorative treatment due to its ease of application, making it suitable for use in a wide range of settings. The Committee considered that inclusion of glass ionomer cement on the Model List, in alignment with WHO's technical guidance on oral health, will support countries to deliver an expanded range of interventions that will benefit the oral health of their populations.

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Silver diamine fluoride – addition – EML and EMLc

Silver diamine fluoride	**ATC Code: N/A**

Proposal

Addition of silver diamine fluoride on the core list of the EML and EMLc for arresting and preventing dental caries in adults and children.

Applicant

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WHO technical department

Noncommunicable Diseases

EML/EMLc

EML and EMLc

Section

30. Dental preparations

Dose form(s) & strength(s)

Solution for topical application: 38% w/v

Core/complementary

Core

Individual/square box listing

Individual

Background (if relevant, e.g. resubmission, previous Expert Committee consideration)

Silver diamine fluoride solution has not previously been considered for inclusion on the Model Lists.

Public health relevance (burden of disease)

The 2017 Global Burden of Disease Study estimated that oral diseases affect close to 3.5 billion people worldwide, with caries of permanent teeth being the most common condition. Globally, 2.3 billion people are estimated to suffer from caries of permanent teeth and more than 530 million children suffer from caries of primary teeth (*1*). Most caries are untreated. The caries burden is very unequal across populations within and between countries, with a clear socioeconomic gradient showing higher disease burden in deprived

and disadvantaged populations who at the same time have less access to care, including preventive care (*2*). Caries is a disease of all age groups with an onset in early childhood and continued increase over the life course. Most significant increases in incidence are observed in adolescent age groups.

Silver diamine fluoride application can arrest the progression of existing dental caries and prevent the incidence of new dental caries by about 80% (*3*). The procedure is painless and arrested carious lesions do not cause further pain and infection (*4*,*5*). Silver diamine fluoride treatment is a minimally invasive alternative for treatment for dental caries and is also indicated for people unable to tolerate conventional treatment due to their specific condition (*6*,*7*). The expected health-related positive effects of silver diamine fluoride treatment include: improved quality of life through reduction of pain and infection from caries, reduced absence from school and work, and substantial cost savings for health systems.

Since the application of silver diamine fluoride on teeth does not require extensive dental training, it can be used to provide people living in rural and remote areas and otherwise disadvantaged populations with access to dental care for caries through the primary health care system (*8*–*10*).

Summary of evidence: benefits (from the application)

A 2019 umbrella review, summarizing 11 systematic reviews, evaluated the evidence on silver diamine fluoride for arresting and preventing root and coronal caries (*4*). Silver diamine fluoride was found to have a positive effect on prevention and arrest of coronal and root caries, consistently outperforming comparators (fluoride varnish, atraumatic restorative treatment and placebo). For root caries prevention, the prevented fraction was 25–71% higher for silver diamine fluoride than placebo. Compared with placebo, silver diamine fluoride was associated with higher prevented fraction for root caries arrest (100–725%), coronal caries prevention (70–78%) and coronal caries arrest (55–96%). Reported caries arrest rates for silver diamine fluoride in primary dentition ranged from 65% to 91%. In comparison, arrest rates for fluoride varnish were 38–44%, for glass ionomer cement were 39–82% and for placebo was 34%.

A 2020 review of systematic reviews found that topical application of silver diamine fluoride was effective in arresting dentinal caries in preschool children, with success rates from 79% to 90% reported in the trials (*3*).

A systematic review and meta-analysis of silver diamine fluoride for controlling caries progression in primary teeth found that application of silver diamine fluoride was more effective than other management options or placebo (*11*). At 12 months, arrest of caries with silver diamine fluoride was 66% higher (95% CI 41 to 91%; $P < 0.00001$) than with other active materials, and 154% higher (95% CI 67 to 85%; $P < 0.00001$) than with placebo.

A systematic review and meta-analysis evaluated the effect of silver diamine fluoride in preventing caries in the primary dentition (*12*). After 2 years of follow-up, application of silver diamine fluoride led to a statistically significant reduction in the development of new dentinal carious lesions compared with placebo or no treatment (weighted mean difference 1.15, prevented fraction 77.5%), and fluoride varnish (weighted mean difference −0.43, prevented fraction 54.0%).

In older adults, silver diamine fluoride has also been found to be effective in arresting and preventing root caries (*13*, *14*). Silver diamine fluoride was found to arrest root caries by 90% after 30 months of follow-up in a randomized trial of annual silver diamine fluoride application in elderly people living in the community (*15*).

Summary of evidence: harms (from the application)

No severe harm and adverse health outcomes due to the application of silver diamine fluoride have been reported.

Silver diamine fluoride application results in a black stain on the arrested dentine caries lesions, which may cause aesthetic concerns (*12*, *16–18*). Tooth pain or gingival irritation, e.g. white lesions on mucosa, gum swelling and gum bleaching, rarely occurred after the application of silver diamine fluoride and subsided rapidly (*16*, *17*). Gingival and mucosa reactions are generally related to insufficient compliance with application protocols, such as incidents of spill-over from the dental cavity.

As pharmacokinetic studies are difficult to conduct in children to test the silver disposition after topical silver diamine fluoride application, a pharmacokinetic model was developed to predict silver disposition in children. The findings showed that the topical application of silver diamine fluoride to prevent or arrest dental caries in children resulted in plasma and tissue silver concentrations lower than the toxic concentration (*19*).

Additional evidence (not in the application)

Not applicable

WHO guidelines

The WHO implementation manual on ending childhood dental caries (*10*) states the following in relation to silver diamine fluoride.

Carious lesions that have progressed to cavitation should be stabilized in order to preserve tooth structure and to prevent negative health consequences such as pain and infection. Annual or semi-annual application of 38% silver diamine fluoride (silver diamine fluoride) solution is effective in arresting the progression of cavitated carious lesions in primary teeth and in hardening these

lesions. The effectiveness of silver diamine fluoride is greater with semi-annual application. This can minimize discomfort and potential pulp damage, and help to keep the caries-affected primary teeth symptomless and functional until their natural exfoliation. This is a painless, simple and low-cost treatment that can be widely promoted as an alternative to conventional invasive caries management techniques, especially in populations and areas with low accessibility to dental care services.

Costs/cost–effectiveness

Topical application of silver diamine fluoride is considered a cost-effective method to prevent and manage dental caries. A study in the United States of America found that silver diamine fluoride treatment as a caries management strategy reduced dental care expenditures within the Medicaid programme by avoiding expensive caries treatment options and preventing complex restorative procedures (*20*). A German study found that silver diamine fluoride application was more cost-effective than chlorhexidine varnish and fluoride rinse. Silver diamine fluoride was considered the most effective and least costly option in populations with a high risk of caries (*21*).

To achieve a high preventive effect (80% prevented fraction), application twice a year is recommended at a total material cost of about US$ 0.20 (*22*, *23*). Since application can be done by community health workers or other trained personnel (non-dentists), the additional implementation costs of programmes using silver diamine fluoride are much lower than other dentist-led forms of fluoride applications.

The retail price of silver diamine fluoride varies by manufacturer and market. Different brands and can be ordered online through different retailers, depending on the country and location.

Availability

Silver diamine fluoride is approved as a class II medical device by the United States Food and Drug Administration.

Silver diamine fluoride is available in several countries around the world, including Argentina, Australia, India, Japan, Thailand and United States of America, and can be ordered online from global distributors. In some countries, national licensing is limited to silver diamine fluoride use for root caries and desensitization.

Other considerations

Not applicable

Committee recommendations

The Expert Committee noted that dental caries of permanent teeth affects 2.3 billion people worldwide and more than 530 million children suffer from caries of primary teeth. Inequalities throughout the life course and across populations in low-, middle- and high-income countries were also noted, with the highest burden in countries with limited resources for prevention and control.

The Expert Committee also noted that primary oral health care in low-resource settings is often limited by a lack of essential supplies such as filling materials or caries preventive agents, a situation which leads to an unnecessary focus of treatment on tooth extraction. The application of silver diamine fluoride is minimally invasive, pain free and particularly suitable for people unable to tolerate conventional invasive dental treatment, such as young children, elderly people, and patients with mental health conditions who may have difficulty cooperating.

The Expert Committee considered the evidence included in the application that showed silver diamine fluoride was effective in arresting dental caries in over 80% of cases, being more effective than other management options or placebo. In addition, with a 2-year follow-up, the application of silver diamine fluoride significantly reduced the development of new dentinal carious lesions compared with placebo, no treatment or fluoride varnish. The Committee noted that silver diamine fluoride also has antibacterial effects (from the silver) and remineralizing effects (from the fluoride).

Evidence on the benefits of silver diamine fluoride in the prevention of dental caries came from a meta-analysis of two small trials that showed positive effects of silver diamine fluoride compared with placebo or no treatment. However, the included trials had important limitations in study design and implementation, reducing the Committee's confidence in the estimates of the benefit of silver diamine fluoride in caries prevention.

The Committee took into account that topical silver diamine fluoride is considered a cost-effective method to prevent and manage dental caries. Moreover, since its application is possible by community health workers or other trained non-dentist personnel, the additional implementation costs of programmes using silver diamine fluoride are much lower than dentist-led fluoride applications.

The Expert Committee, therefore, recommended the listing of silver diamine fluoride on the core list of the EML and EMLc in the new section for dental preparations for the treatment of dental caries on the basis of its relevant benefits in arresting dental caries. The Committee considered that inclusion of silver diamine fluoride on the Model List, in alignment with WHO technical guidance on oral health, will support countries to deliver an expanded range of interventions that will benefit the oral health of their populations.

The Committee did not recommend the listing of silver diamine fluoride for use in prevention due to uncertainty in the estimates of benefit. The Committee would welcome new evidence supporting its use in prevention of dental caries for consideration in the future.

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Annex 1

WHO Model List of Essential Medicines – 22nd List (2021)

Explanatory notes

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

Where the **[c]** symbol is placed next to an individual medicine or strength of medicine on the core list it signifies that there is a specific indication for restricting its use to children.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

Where the ***[c]*** symbol is placed next to an individual medicine or strength of medicine on the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

The **square box symbol** (□) is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the Anatomical Therapeutic Chemical (ATC) classification, which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square box listings are applicable to medicine selection for children. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO website https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance.

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia*. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 *Inhalational medicines*

halothane	**Inhalation.**
isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medical gas).

1.1.2 *Injectable medicines*

ketamine	**Injection:** 50 mg/mL (as hydrochloride) in 10 mL vial.
☐ propofol Therapeutic alternatives: – thiopental	**Injection:** 10 mg/mL; 20 mg/mL.

1.2 Local anaesthetics

☐ bupivacaine Therapeutic alternatives to be reviewed (2023)	**Injection:** 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine Therapeutic alternatives to be reviewed (2023)	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
Complementary List	
ephedrine	***Injection:** 30 mg/mL (hydrochloride) in 1 mL ampoule.* *(For use in spinal anaesthesia during delivery, to prevent hypotension).*

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*	
1.3 Preoperative medication and sedation for short-term procedures	
atropine	**Injection:** 1 mg (sulfate) in 1 mL ampoule.
☐ midazolam Therapeutic alternatives to be reviewed (2023)	**Injection:** 1 mg/mL. **Oral liquid:** 2 mg/mL [c]. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection:** 10 mg (sulfate or hydrochloride) in 1 mL ampoule.
1.4 Medical gases	
oxygen*	**Inhalation** For use in the management of hypoxaemia. * No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.
2. MEDICINES FOR PAIN AND PALLIATIVE CARE	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)	
acetylsalicylic acid	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg.
ibuprofen [a]	**Oral liquid:** 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol*	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Suppository:** 100 mg. **Tablet:** 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
2.2 Opioid analgesics	
codeine	**Tablet:** 30 mg (phosphate).
fentanyl*	**Transdermal patch:** 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr * For the management of cancer pain
☐ morphine Therapeutic alternatives: – hydrormorphone – oxycodone	**Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. **Oral liquid:** 10 mg (morphine hydrochloride or morphine sulfate)/5 mL. **Tablet (slow release):** 10 mg to 200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate).
Complementary list	
*methadone**	***Tablet:** 5 mg; 10 mg (hydrochloride)* ***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL (hydrochloride)* ***Concentrate for oral liquid:** 5 mg/mL; 10 mg/mL (hydrochloride)* ** For the management of cancer pain.*
2.3 Medicines for other common symptoms in palliative care	
amitriptyline	**Tablet:** 10 mg; 25 mg; 75 mg.
cyclizine [c]	**Injection:** 50 mg/mL. **Tablet:** 50 mg.
dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. **Oral liquid:** 2 mg/5 mL. **Tablet:** 2 mg [c]; 4 mg.
diazepam	**Injection:** 5 mg/mL. **Oral liquid:** 2 mg/5 mL. **Rectal solution:** 2.5 mg; 5 mg; 10 mg. **Tablet:** 5 mg; 10 mg.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
docusate sodium	**Capsule:** 100 mg. **Oral liquid:** 50 mg/5 mL.
fluoxetine [a]	**Solid oral dosage form:** 20 mg (as hydrochloride). [a] > 8 years.
haloperidol	**Injection:** 5 mg in 1 mL ampoule. **Oral liquid:** 2 mg/mL. **Solid oral dosage form:** 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	**Injection:** 20 mg/mL.
hyoscine hydrobromide [c]	**Injection:** 400 micrograms/mL; 600 micrograms/mL. **Transdermal patches:** 1 mg/72 hours.
lactulose [c]	**Oral liquid:** 3.1 to 3.7 g/5 mL.
loperamide	**Solid oral dosage form:** 2 mg.
metoclopramide	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL. **Solid oral form:** 10 mg (hydrochloride).
midazolam	**Injection:** 1 mg/mL; 5 mg/mL. **Oral liquid:** 2mg/mL [c]. **Solid oral dosage form:** 7.5 mg; 15 mg.
☐ ondansetron [a] Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg base/mL in 2 mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] > 1 month.
senna	**Oral liquid:** 7.5 mg/5 mL.
3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS *(continued)*	
☐ loratadine*	**Oral liquid:** 1 mg/mL.
Therapeutic alternatives:	**Tablet:** 10 mg.
– cetirizine – fexofenadine	* *There may be a role for sedating antihistamines for limited indications (EMLc).*
☐ prednisolone	**Oral liquid:** 5 mg/mL [c].
Therapeutic alternatives:	**Tablet:** 5 mg; 25 mg.
– prednisone	

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Powder.**
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/mL in 10 mL ampoule. **Oral liquid:** 10% [c]; 20% [c].
atropine	**Injection:** 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	**Injection:** 100 mg/mL in 10 mL ampoule.
methylthioninium chloride (methylene blue)	**Injection:** 10 mg/mL in 10 mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1 mL ampoule.
penicillamine	**Solid oral dosage form:** 250 mg.
potassium ferric hexacyano-ferrate(II) -2H_2O (Prussian blue)	**Powder for oral administration.**
sodium nitrite	**Injection:** 30 mg/mL in 10 mL ampoule.
sodium thiosulfate	**Injection:** 250 mg/mL in 50 mL ampoule.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:*** *50 mg/mL in 2 mL ampoule.*
fomepizole	***Injection:*** *5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.*
sodium calcium edetate	***Injection:*** *200 mg/mL in 5 mL ampoule.*
succimer	***Solid oral dosage form:*** *100 mg.*

5. ANTICONVULSANTS/ANTIEPILEPTICS

carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg.
diazepam	**Gel or rectal solution:** 5 mg/mL in 0.5 mL; 2 mL; 4 mL tubes.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. * For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
☐ lorazepam Therapeutic alternatives: – diazepam (injection) – midazolam (injection)	**Injection:** 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
magnesium sulfate*	**Injection:** 0.5 g/mL in 2 mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume). * For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
midazolam	**Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL. **Ampoule*:** 1 mg/mL; 10 mg/mL. * For buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 200 mg/mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/mL (sodium) in 5 mL vial. **Oral liquid:** 25 mg to 30 mg/5 mL.* **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium). **Tablet (chewable):** 50 mg. * The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.

5. ANTICONVULSANTS/ANTIEPILEPTICS *(continued)*	
valproic acid (sodium valproate)* * *Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg.
Complementary List	
ethosuximide	***Capsule:** 250 mg.* ***Oral liquid:** 250 mg/5 mL.*
*valproic acid (sodium valproate)** * *Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*	***Injection:** 100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule.*
6. ANTI-INFECTIVE MEDICINES	
6.1 Anthelminthics	
6.1.1 *Intestinal anthelminthics*	
albendazole	**Tablet (chewable):** 400 mg.
ivermectin	**Tablet (scored):** 3 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 600 mg.
pyrantel	**Oral liquid:** 50 mg/mL (as embonate or pamoate). **Tablet (chewable):** 250 mg (as embonate or pamoate).

6. ANTI-INFECTIVE MEDICINES *(continued)*	
6.1.2 ***Antifilarials***	
albendazole	**Tablet (chewable):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet (scored):** 3 mg.
6.1.3 ***Antischistosomals and other antitrematode medicines***	
praziquantel	**Tablet:** 600 mg.
triclabendazole	**Tablet:** 250 mg.
Complementary List	
*oxamniquine**	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.* ** For use when praziquantel treatment fails.*
6.1.4 ***Cysticidal medicines***	
Complementary List	
albendazole	***Tablet (chewable):*** *400 mg.*
mebendazole	***Tablet (chewable)****: 500 mg.*
praziquantel	***Tablet:*** *500 mg; 600 mg.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.1 *Access group antibiotics*

amikacin

Injection: 250 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *High-risk febrile neutropenia* – *Pyelonephritis or prostatitis (severe)*	– *Sepsis in neonates and children* [c]

amoxicillin

Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate) [c].

Solid oral dosage form: 250 mg; 500 mg; 1g (as trihydrate).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (mild to moderate)* – *Community acquired pneumonia (severe)* [c] – *Complicated severe acute malnutrition* [c] – *Exacerbations of COPD* – *Otitis media* – *Pharyngitis* – *Progressive apical dental abscess* – *Sepsis in neonates and children* [c] – *Sinusitis* – *Uncomplicated severe acute malnutrition* [c]	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

amoxicillin + clavulanic acid

Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.

Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c].

Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt); 875 mg (as trihydrate) + 125 mg (as potassium salt).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* [c] – *Complicated intraabdominal infections (mild to moderate)* – *Exacerbations of COPD* – *Hospital acquired pneumonia* – *Low-risk febrile neutropenia* – *Lower urinary tract infections* – *Sinusitis* – *Skin and soft tissue infections*	– *Bone and joint infections* – *Community-acquired pneumonia (mild to moderate)* – *Community acquired pneumonia (severe)* – *Otitis media* – *Surgical prophylaxis*

ampicillin

Powder for injection: 500 mg; 1 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* [c] – *Complicated intraabdominal infections* [c] – *Complicated severe acute malnutrition* [c] – *Sepsis in neonates and children* [c]	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

benzathine benzylpenicillin

Powder for injection: 1.2 million IU (≈ 900 mg) in vial [c]; 2.4 million IU (≈ 1.8 g) in vial.

FIRST CHOICE	SECOND CHOICE
– *Syphilis*	

benzylpenicillin

Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* [c] – *Complicated severe acute malnutrition* [c] – *Sepsis in neonates and children* [c] – *Syphilis*	– *Acute bacterial meningitis* [c]

cefalexin

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (anhydrous).

Solid oral dosage form: 250 mg; 500 mg (as monohydrate).

FIRST CHOICE	SECOND CHOICE
– *Skin and soft tissue infections*	– *Exacerbations of COPD* – *Pharyngitis*

cefazolin [a]

Powder for injection: 1 g (as sodium salt) in vial.

[a] > 1 month.

FIRST CHOICE	SECOND CHOICE
– *Surgical prophylaxis*	– *Bone and joint infections*

chloramphenicol

Capsule: 250 mg.

Oily suspension for injection*: 0.5 g/mL (as sodium succinate) in 2 mL ampoule.

* Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults.

Oral liquid: 150 mg/5 mL (as palmitate).

Powder for injection: 1 g (sodium succinate) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

clindamycin

Capsule: 150 mg (as hydrochloride).

Injection: 150 mg/mL (as phosphate); 600 mg/4 mL (as phosphate); 900 mg/6 mL (as phosphate).

Oral liquid: 75 mg/5 mL (as palmitate) [c].

FIRST CHOICE	SECOND CHOICE
– *Necrotizing fasciitis*	– *Bone and joint infections*

☐ cloxacillin*

Therapeutic alternatives:

– 4th level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)

Capsule: 500 mg; 1 g (as sodium).

Powder for injection: 500 mg (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL (as sodium).

* cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
– *Bone and joint infections* – *Skin and soft tissue infections*	– *Sepsis in neonates and children* [c]

doxycycline [a]

Oral liquid: 25 mg/5 mL [c]; 50 mg/5 mL (anhydrous) [c].

Powder for injection: 100 mg in vial.

Solid oral dosage form: 50 mg [c]; 100 mg (as hyclate).

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

FIRST CHOICE	SECOND CHOICE
– *Cholera* – *Sexually transmitted infection due to Chlamydia trachomatis*	– *Cholera* [c] – *Community acquired pneumonia (mild to moderate)* – *Exacerbations of COPD*

6. ANTI-INFECTIVE MEDICINES *(continued)*

gentamicin

Injection: 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis in neonates* [c] – *Community acquired pneumonia (severe)* [c] – *Complicated intraabdominal infections* [c] – *Complicated severe acute malnutrition* [c] – *Sepsis in neonates and children* [c]	– *Gonorrhoea* – *Surgical prophylaxis*

metronidazole

Injection: 500 mg in 100 mL vial.

Oral liquid: 200 mg/5 mL (as benzoate).

Suppository: 500 mg; 1 g.

Tablet: 200 mg to 500 mg.

FIRST CHOICE	SECOND CHOICE
– *C. difficile infection* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intrabdominal infections (severe)* – *Necrotizing fasciitis* – *Surgical prophylaxis* – *Trichomoniasis*	– *Complicated intraabdominal infections (mild to moderate)*

nitrofurantoin

Oral liquid: 25 mg/5 mL [c].

Tablet: 100 mg.

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

phenoxymethylpenicillin

Powder for oral liquid: 250 mg/5 mL (as potassium).

Tablet: 250 mg; 500 mg (as potassium).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (mild to moderate)* – *Pharyngitis* – *Progressive apical dental abscess*	

procaine benzylpenicillin*

Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial.

* Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.

FIRST CHOICE	SECOND CHOICE
– *Syphilis (congenital)* [c]	– *Syphilis*

spectinomycin

Powder for injection: 2 g (as hydrochloride) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Gonorrhoea*

sulfamethoxazole + trimethoprim

Injection: 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule.

Oral liquid: 200 mg + 40 mg/5 mL.

Tablet: 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	– *Acute invasive diarrhoea / bacterial dysentery*

trimethoprim

Tablet: 100 mg; 200 mg.

Oral liquid: 50 mg/5 mL [c].

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.2 ***Watch group antibiotics***

azithromycin

Capsule: 250 mg; 500 mg (anhydrous).

Oral liquid: 200 mg/5 mL.

FIRST CHOICE	SECOND CHOICE
– *Cholera* [c] – *Enteric fever* – *Gonorrhoea* – *Sexually transmitted infection due to Chlamydia trachomatis* – *Trachoma* – *Yaws*	– *Acute invasive bacterial diarrhoea / dysentery* – *Gonorrhoea*

cefixime

Powder for oral liquid: 100 mg/5 mL [c].

Solid oral dosage form: 200 mg; 400 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
	– *Acute invasive bacterial diarrhoea / dysentery* – *Gonorrhoea*

cefotaxime*

Powder for injection: 250 mg (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intraabdominal infections (severe)* – *Hospital acquired pneumonia* – *Pyelonephritis or prostatitis (severe)*	– *Bone and joint infections* – *Pyelonephritis or prostatitis (mild to moderate)* – *Sepsis in neonates and children* [c]

6. ANTI-INFECTIVE MEDICINES *(continued)*

ceftriaxone* [a]

Powder for injection: 250 mg; 1 g; 2 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intrabdominal infections (severe)* – *Endophthalmitis* – *Enteric fever* – *Gonorrhoea* – *Hospital acquired pneumonia* – *Necrotizing fasciitis* – *Pyelonephritis or prostatitis (severe)*	– *Acute invasive bacterial diarrhoea / dysentery* – *Bone and joint infections* – *Pyelonephritis or prostatitis (mild to moderate)* – *Sepsis in neonates and children* [c]

cefuroxime

Powder for injection: 250 mg; 750 mg; 1.5 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Surgical prophylaxis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

ciprofloxacin

Oral liquid: 250 mg/5 mL (anhydrous) [c].

Solution for IV infusion: 2 mg/mL (as hyclate) [c].

Solid oral dosage form: 250 mg; 500 mg (as hydrochloride).

FIRST CHOICE	SECOND CHOICE
– *Acute invasive bacterial diarrhoea / dysentery* – *Enteric fever* – *Low-risk febrile neutropenia* – *Pyelonephritis or prostatitis (mild to moderate)*	– *Cholera* – *Complicated intraabdominal infections (mild to moderate)*

☐ clarithromycin†

Therapeutic alternatives:

– erythromycin*

* as second choice treatment for pharyngitis in children (EMLc only)

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL.

Powder for injection: 500 mg in vial.

Solid oral dosage form: 500 mg.

† clarithromycin is also listed for use in combination regimens for eradication of *H. pylori* in adults.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)*	– *Pharyngitis*

piperacillin + tazobactam

Powder for injection: 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Complicated intraabdominal infections (severe)* – *High-risk febrile neutropenia* – *Hospital acquired pneumonia* – *Necrotizing fasciitis*	

vancomycin

Capsule: 125 mg; 250 mg (as hydrochloride).

FIRST CHOICE	SECOND CHOICE
	– *C. difficile infection*

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

ceftazidime

Powder for injection: *250 mg; 1 g (as pentahydrate) in vial.*

FIRST CHOICE	SECOND CHOICE
– *Endophthalmitis*	

☐ *meropenem** [a]

Powder for injection: *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*

[a] > 3 months.

Therapeutic alternatives:*

– *imipenem + cilastatin*

* *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.*

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis in neonates* [c] – *Complicated intraabdominal infections (severe)* – *High-risk febrile neutropenia*

vancomycin

Powder for injection: *250 mg; 500 mg; 1 g (as hydrochloride) in vial.*

FIRST CHOICE	SECOND CHOICE
– *Endophthalmitis* – *Necrotizing fasciitis*	– *High-risk febrile neutropenia*

6.2.3 *Reserve group antibiotics*

Complementary List

cefiderocol

Powder for injection: *1 g (as sulfate toxylate) in vial.*

ceftazidime + avibactam

Powder for injection: *2 g + 0.5 g in vial.*

colistin

Powder for injection: *1 million IU (as colistemethate sodium) in vial.*

fosfomycin

Powder for injection: *2 g; 4 g (as sodium) in vial.*

linezolid

Injection for intravenous administration: *2 mg/mL in 300 mL bag.*

Powder for oral liquid: *100 mg/5 mL.*

Tablet: *400 mg; 600 mg.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

meropenem + vaborbactam	***Powder for injection:*** *1 g (as trihydrate) + 1 g in vial.*
plazomicin	***Injection:*** *500 mg/10 mL.*
polymyxin B	***Powder for injection:*** *500,000 IU in vial.*

6.2.4 ***Antileprosy medicines***

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Capsule:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Solid oral dosage form:** 150 mg; 300 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.5 *Antituberculosis medicines*

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	**Oral liquid:** 25 mg/mL [c]. **Tablet:** 100 mg; 400 mg (hydrochloride). **Tablet (dispersible):** 100 mg [c].
ethambutol + isoniazid + pyrazinamide + rifampicin	**Tablet:** 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	**Tablet:** 275 mg + 75 mg + 150 mg.
isoniazid	**Oral liquid:** 50 mg/5 mL [c]. **Tablet:** 100 mg; 300 mg. **Tablet (dispersible):** 100 mg [c].
isoniazid + pyrazinamide + rifampicin	**Tablet (dispersible):** 50 mg + 150 mg + 75 mg [c].
isoniazid + rifampicin	**Tablet:** 75 mg + 150 mg; 150 mg + 300 mg. **Tablet (dispersible):** 50 mg + 75 mg [c].
isoniazid + rifapentine	**Tablet (scored):** 300 mg + 300 mg.
moxifloxacin	**Tablet:** 400 mg.
pyrazinamide	**Oral liquid:** 30 mg/mL [c]. **Tablet:** 400 mg; 500 mg **Tablet (dispersible):** 150 mg.
rifabutin	**Solid oral dosage form:** 150 mg.* * For use only in patients with HIV receiving protease inhibitors.
rifampicin	**Oral liquid:** 20 mg/mL [c]. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine	**Tablet:** 150 mg; 300 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin	***Injection:*** *100 mg/2 mL (as sulfate) in 2 mL vial; 250 mg/mL (as sulfate) in 2 mL vial.*
*amoxicillin + clavulanic acid**	***Powder for oral liquid:*** *250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL* [c] *.* ***Tablet:*** *500 mg (as trihydrate) + 125 mg (as potassium salt).* * *For use only in combination with meropenem or imipenem+cilastatin.*
bedaquiline [a]	***Tablet:*** *20 mg* [c] *; 100 mg.* [a] ≥ 5 years
clofazimine	***Solid oral dosage form:*** *50 mg; 100 mg.*
☐ *cycloserine* *Therapeutic alternatives:* *– terizidone*	***Solid oral dosage form:*** *125 mg* [c] *; 250 mg.*
delamanid [a]	***Tablet (dispersible):*** *25 mg* [c] *.* [a] ≥ 3 years ***Tablet:*** *50 mg.* [a] ≥ 6 years
☐ *ethionamide* *Therapeutic alternatives:* *– protionamide*	***Tablet:*** *125 mg; 250 mg.* ***Tablet (dispersible):*** *125 mg* [c] *.*
levofloxacin	***Tablet:*** *250mg; 500 mg; 750 mg.* ***Tablet (dispersible):*** *100 mg* [c] *.*
linezolid	***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *600 mg.* ***Tablet (dispersible):*** *150 mg* [c] *.*
☐ *meropenem* *Therapeutic alternatives:* *– imipenem + cilastatin*	***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*
moxifloxacin	***Tablet:*** *400 mg.* ***Tablet (dispersible):*** *100 mg* [c] *.*
p-aminosalicylic acid	***Granules:*** *4 g in sachet.*
streptomycin [c]	***Powder for injection:*** *1 g (as sulfate) in vial.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.3 Antifungal medicines

amphotericin B	**Powder for injection:** 50 mg (as sodium deoxycholate or liposomal complex) in vial.
clotrimazole	**Vaginal cream:** 1%; 10%. **Vaginal tablet:** 100 mg; 500 mg.
fluconazole	**Capsule:** 50 mg. **Injection:** 2 mg/mL in vial. **Oral liquid:** 50 mg/5 mL.
flucytosine	**Capsule:** 250 mg. **Infusion:** 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL [c]. **Solid oral dosage form:** 125 mg; 250 mg.
itraconazole*	**Capsule:** 100 mg. **Oral liquid:** 10 mg/mL. * For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 50 mg/5 mL [c]; 100 000 IU/mL [c]. **Pessary:** 100 000 IU. **Tablet:** 100 000 IU; 500 000 IU.
voriconazole*	**Tablet:** 50 mg; 200 mg **Powder for injection:** 200 mg in vial **Powder for oral liquid:** 40 mg/mL * For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.

Complementary List

☐ *micafungin* *Therapeutic alternatives:* – *anidulafungin* – *caspofungin*	***Powder for injection:*** *50 mg (as sodium); 100 mg (as sodium) in vial.*
potassium iodide	***Saturated solution.***

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4 Antiviral medicines

6.4.1 *Antiherpes medicines*

☐ aciclovir	**Oral liquid:** 200 mg/5 mL [c].
Therapeutic alternatives: – valaciclovir (oral)	**Powder for injection:** 250 mg (as sodium salt) in vial. **Tablet:** 200 mg.

6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission, pre-exposure prophylaxis (where indicated) and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

abacavir	**Tablet:** 300 mg (as sulfate).
lamivudine	**Oral liquid:** 50 mg/5 mL [c]. **Tablet:** 150 mg.
tenofovir disoproxil fumarate†	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). † also indicated for pre-exposure prophylaxis.
zidovudine	**Capsule:** 250 mg. **Oral liquid:** 50 mg/5 mL. **Solution for IV infusion:** 10 mg/mL in 20 mL vial. **Tablet:** 300 mg.

6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

efavirenz	**Tablet:** 600 mg.
nevirapine [a]	**Oral liquid:** 50 mg/5 mL. **Tablet:** 50 mg (dispersible); 200 mg. [a] > 6 weeks

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.3 ***Protease inhibitors***

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir + ritonavir	**Tablet (heat stable):** 300 mg (as sulfate) + 100 mg.
darunavir [a]	**Tablet:** 75 mg; 400 mg; 600 mg; 800 mg [a] > 3 years
lopinavir + ritonavir	**Solid oral dosage form:** 40 mg + 10 mg [c]. **Tablet (heat stable):** 100 mg + 25 mg; 200 mg + 50 mg.
ritonavir	**Tablet (heat stable):** 25 mg; 100 mg.

6.4.2.4 ***Integrase inhibitors***

dolutegravir [a]	**Tablet (dispersible, scored):** 10 mg [c]. [a] ≥ 4 weeks and ≥ 3 kg **Tablet:** 50 mg [a] ≥ 25 kg
raltegravir*	**Granules for oral suspension:** 100 mg in sachet. **Tablet (chewable):** 25 mg. **Tablet:** 400 mg. * For use in pregnant women and in second-line regimens in accordance with WHO treatemnt guidelines.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
6.4.2.5 ***Fixed-dose combinations of antiretroviral medicines***	
abacavir + lamivudine	**Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg.
dolutegravir + lamivudine + tenofovir	**Tablet:** 50 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
efavirenz + ☐ emtricitabine + tenofovir Therapeutic alternatives: – lamivudine (for emtricitabine)	**Tablet:** 600 mg + 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
efavirenz + lamivudine + tenofovir	**Tablet:** 400 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
☐ emtricitabine + tenofovir† Therapeutic alternatives: – lamivudine (for emtricitabine)	**Tablet:** 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). † combination also indicated for pre-exposure prophylaxis
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg [c]; 150 mg + 300 mg.
6.4.2.6 ***Medicines for prevention of HIV-related opportunistic infections***	
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
6.4.3 ***Other antivirals***	
ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10 mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of viral haemorrhagic fevers.
valganciclovir*	**Tablet:** 450 mg. * For the treatment of cytomegalovirus retinitis (CMVr).
Complementary list	
*oseltamivir**	***Capsule:*** *30 mg; 45 mg; 75 mg (as phosphate).* * *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.*
*valganciclovir** ***[c]***	***Powder for oral solution:*** *50 mg/mL* ***Tablet:*** *450 mg.* * *For the treatment of cytomegalovirus retinitis (CMVr).*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4 Antihepatitis medicines

6.4.4.1 *Medicines for hepatitis B*

6.4.4.1.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

entecavir	**Oral liquid:** 0.05 mg/mL **Tablet:** 0.5 mg; 1 mg
tenofovir disoproxil fumarate	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).

6.4.4.2 *Medicines for hepatitis C*

Pangenotypic direct-acting antivirals should be considered as therapeutic alternatives for the purposes of selection and procurement at national level.

6.4.4.2.1 ☐ *Pangenotypic direct-acting antiviral combinations*

daclatasvir*	**Tablet:** 30 mg; 60 mg (as hydrochloride). * Pangenotypic when used in combination with sofosbuvir.
daclatasvir + sofosbuvir	**Tablet:** 60 mg + 400 mg.
glecaprevir + pibrentasvir	**Tablet:** 100 mg + 40 mg. **Granules:** 50 mg + 20 mg in sachet [c].
sofosbuvir*	**Tablet:** 200 mg; 400 mg. * Pangenotypic when used in combination with daclatasvir.
sofosbuvir + velpatasvir	**Tablet:** 200 mg + 50 mg [c]; 400 mg + 100 mg.

6.4.4.2.2 *Non-pangenotypic direct-acting antiviral combinations*

dasabuvir	**Tablet:** 250 mg.
ledipasvir + sofosbuvir	**Tablet:** 90 mg + 400 mg.
ombitasvir + paritaprevir + ritonavir	**Tablet:** 12.5 mg + 75 mg + 50 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4.2.3 ***Other antivirals for hepatitis C***

ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10 mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of hepatitis C, in combination with direct acting anti-viral medicines.
Complementary list	
*pegylated interferon alfa (2a or 2b)**	***Vial or pre-filled syringe:*** *180 micrograms (peginterferon alfa-2a).* *80 micrograms, 100 micrograms (peginterferon alfa-2b).* * *To be used in combination with ribavirin.*

6.5 Antiprotozoal medicines

6.5.1 ***Antiamoebic and antigiardiasis medicines***

diloxanide [a]	**Tablet:** 500 mg (furoate). [a] > 25 kg.
☐ metronidazole	**Injection:** 500 mg in 100 mL vial.
Therapeutic alternatives: – tinidazole	**Oral liquid:** 200 mg/5 mL (as benzoate). **Tablet:** 200 mg to 500 mg.

6.5.2 ***Antileishmaniasis medicines***

amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as sulfate).
sodium stibogluconate **or** meglumine antimoniate	**Injection:** 100 mg/mL, 1 vial = 30 mL **or** 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5 mL ampoule.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.3 *Antimalarial medicines*

6.5.3.1 *For curative treatment*

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs) in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
artemether*	**Oily injection:** 80 mg/mL in 1 mL ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg [c]. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Rectal dosage form:** 50 mg [c]; 100 mg [c]; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [c]. **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
artesunate + amodiaquine*	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. * Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
artesunate + pyronaridine tetraphosphate [a]	**Granules:** 20 mg + 60 mg [c]. **Tablet:** 60 mg + 180 mg. [a] > 5 kg

6. ANTI-INFECTIVE MEDICINES *(continued)*	
chloroquine*	**Oral liquid:** 50 mg/5 mL (as phosphate or sulfate). **Tablet:** 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of *Plasmodium vivax* infection.
dihydroartemisinin + piperaquine phosphate [a]	**Tablet:** 20 mg + 160 mg; 40 mg + 320 mg. [a] > 5 kg
doxycycline*	**Capsule:** 100 mg (as hydrochloride or hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *Plasmodium vivax* and *Plasmodium ovale* infections, given for 14 days.
quinine*	**Injection:** 300 mg/mL (hydrochloride) in 2 mL ampoule. **Tablet:** 300 mg (sulfate) or 300 mg (bisulfate). * For use only in the management of severe malaria and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	**Tablet:** 500 mg + 25 mg. * Only in combination with artesunate 50 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.3.2 ***For chemoprevention***

amodiaquine – sulfadoxine + pyrimethamine [c]	**Co-packaged dispersible tablets:** amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	**Oral liquid:** 50 mg/5 mL (as phosphate or sulfate). **Tablet:** 150 mg (as phosphate or sulfate). * For use only in central American regions, for *Plasmodium vivax* infections.
doxycycline [a]	**Solid oral dosage form:** 100 mg (as hydrochloride or hyclate). [a] > 8 years.
mefloquine [a]	**Tablet:** 250 mg (as hydrochloride). [a] > 5 kg or > 3 months.
proguanil*	**Tablet:** 100 mg (as hydrochloride). * For use only in combination with chloroquine.
sulfadoxine + pyrimethamine	**Tablet:** 250 mg + 12.5 mg [c]; 500 mg + 25 mg.

6.5.4 ***Antipneumocystosis and antitoxoplasmosis medicines***

pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL [c]. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg [c]; 800 mg + 160 mg
Complementary List	
pentamidine	***Tablet:*** *200 mg; 300 mg (as isethionate).*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.5 *Antitrypanosomal medicines*

6.5.5.1 *African trypanosomiasis*

fexinidazole*	**Tablet:** 600 mg * For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine*	**Powder for injection:** 200 mg (as isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	**Powder for injection:** 1 g in vial. * To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg/mL (hydrochloride) in 100 mL bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
melarsoprol	**Injection:** 180 mg/5 mL in 5 mL ampoule (3.6% solution).
nifurtimox*	**Tablet:** 120 mg. * Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

Complementary List

melarsoprol ***[c]***	***Injection:*** *180 mg/5 mL in 5 mL ampoule (3.6% solution).*

6.5.5.2 *American trypanosomiasis*

benznidazole	**Tablet:** 12.5 mg **[c]**; 100 mg. **Tablet (scored):** 50 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg; 250 mg.

6.6 Medicines for ectoparasitic infections

ivermectin	**Tablet (scored):** 3 mg

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

acetylsalicylic acid	**Tablet:** 300 mg to 500 mg.
ibuprofen [c]	**Tablet:** 200 mg; 400 mg.
paracetamol	**Oral liquid:** 120 mg/5 mL [c]; 125 mg/5 mL [c]. **Tablet:** 300 mg to 500 mg.
sumatriptan	**Tablet:** 50 mg

7.2 For prophylaxis

☐ propranolol Therapeutic alternatives to be reviewed (2023)	**Tablet:** 20 mg; 40 mg (hydrochloride).

8. IMMUNOMODULATORS AND ANTINEOPLASTICS

8.1 Immunomodulators for non-malignant disease

Complementary List

☐ *adalimumab**	***Injection:*** *40 mg/0.8 mL; 40 mg/0.4 mL.*
Therapeutic alternatives:* – *certolizumab pegol* – *etanercept* – *golimumab* – *infliximab* * *including quality-assured biosimilars*	
azathioprine	***Powder for injection:*** *100 mg (as sodium salt) in vial.* ***Tablet (scored):*** *50 mg.*
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/mL in 1 mL ampoule.*
tacrolimus	***Capsule (immediate-release):*** *0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg.* ***Granules for oral supsension:*** *0.2 mg; 1 mg.* ***Injection:*** *5 mg/mL in 1 mL vial.*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2 Antineoplastics and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

8.2.1 *Cytotoxic medicines*

Complementary List

arsenic trioxide	***Concentrate for solution for infusion:*** *1 mg/mL* – *Acute promyelocytic leukaemia*
*asparaginase**	***Powder for injection:*** *10 000 IU in vial.* – *Acute lymphoblastic leukaemia*
* *including quality-assured biosimilars*	
bendamustine	***Injection:*** *45 mg/0.5 mL; 180 mg/2 mL.* – *Chronic lymphocytic leukaemia* – *Follicular lymphoma*
bleomycin	***Powder for injection:*** *15 mg (as sulfate) in vial.* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*
calcium folinate	***Injection:*** *3 mg/mL in 10 mL ampoule.* ***Tablet:*** *5 mg; 15 mg; 25 mg.* – *Burkitt lymphoma* – *Early stage colon cancer* – *Early stage rectal cancer* – *Gestational trophoblastic neoplasia* – *Metastatic colorectal cancer* – *Osteosarcoma*
capecitabine	***Tablet:*** *150 mg; 500 mg.* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic breast cancer* – *Metastatic colorectal cancer*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* – *Cervical cancer* – *Early stage breast cancer* – *Epithelial ovarian cancer* – *Head and neck cancer (as a radio-sensitizer)* – *Low-grade glioma* – *Nasopharyngeal cancer* – *Nephroblastoma (Wilms tumour)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Retinoblastoma* – *Testicular germ cell tumour*
chlorambucil	***Tablet:*** *2 mg.* – *Chronic lymphocytic leukaemia*
cisplatin	***Injection:*** *10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100 mL.* – *Cervical cancer* – *Head and neck cancer (as a radio-sensitizer)* – *Low-grade glioma* – *Nasopharyngeal cancer (as a radio-sensitizer)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*
cyclophosphamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* ***Tablet:*** *25 mg, 50 mg.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Chronic lymphocytic leukaemia* – *Diffuse large B-cell lymphoma* – *Early stage breast cancer* – *Ewing sarcoma* – *Follicular lymphoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Low-grade glioma* – *Metastatic breast cancer* – *Multiple myeloma* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
cytarabine	***Powder for injection:*** *100 mg in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Acute promyelocytic leukaemia* – *Burkitt lymphoma.*
dacarbazine	***Powder for injection:*** *100 mg in vial.* – *Hodgkin lymphoma*
dactinomycin	***Powder for injection:*** *500 micrograms in vial.* – *Ewing sarcoma* – *Gestational trophoblastic neoplasia* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
daunorubicin	***Powder for injection:*** *50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Acute promyelocytic leukaemia*
docetaxel	***Injection:*** *20 mg/mL; 40 mg/mL.* – *Early stage breast cancer* – *Metastatic breast cancer* – *Metastatic prostate cancer*
doxorubicin	***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Early stage breast cancer* – *Ewing sarcoma* – *Follicular lymphoma* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Metastatic breast cancer* – *Multiple myeloma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
etoposide	***Capsule:*** *50 mg, 100 mg.* ***Injection:*** *20 mg/mL in 5 mL ampoule.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Burkitt lymphoma* – *Ewing sarcoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Nephroblastoma (Wilms tumour)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Retinoblastoma* – *Testicular germ cell tumour*
fludarabine	***Powder for injection:*** *50 mg (phosphate) in vial.* ***Tablet:*** *10 mg* – *Chronic lymphocytic leukaemia.*
fluorouracil	***Injection:*** *50 mg/mL in 5 mL ampoule.* – *Early stage breast cancer* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic colorectal cancer* – *Nasopharyngeal cancer*
gemcitabine	***Powder for injection:*** *200 mg; 1 g in vial.* – *Epithelial ovarian cancer* – *Non-small cell lung cancer*
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g* – *Chronic myeloid leukaemia*
ifosfamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Ovarian germ cell tumour* – *Osteosarcoma* – *Rhabdomyosarcoma* – *Testicular germ cell tumour*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
irinotecan	***Injection:*** *40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.* – *Metastatic colorectal cancer* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
melphalan	***Tablet:*** *2 mg.* ***Powder for injection:*** *50 mg in vial.* – *Multiple myeloma*
mercaptopurine	***Tablet:*** *50 mg.* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia*
methotrexate	***Powder for injection:*** *50 mg (as sodium salt) in vial.* ***Tablet:*** *2.5 mg (as sodium salt).* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia* – *Burkitt lymphoma* – *Early stage breast cancer* – *Gestational trophoblastic neoplasia* – *Osteosarcoma*
oxaliplatin	***Injection:*** *50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.* ***Powder for injection:*** *50 mg; 100 mg in vial.* – *Early stage colon cancer* – *Metastatic colorectal cancer*
paclitaxel	***Injection:*** *6 mg/mL in vial.* – *Cervical cancer* – *Epithelial ovarian cancer* – *Early stage breast cancer* – *Metastatic breast cancer* – *Kaposi sarcoma* – *Nasopharyngeal cancer* – *Non-small cell lung cancer* – *Ovarian germ cell tumour*
*pegaspargase**	***Injection:*** *3,750 units/5 mL in vial.*
* *including quality-assured biosimilars*	– *Acute lymphoblastic leukaemia*
procarbazine [c]	***Capsule:*** *50 mg (as hydrochloride).* – *Hodgkin lymphoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
realgar-Indigo naturalis formulation	***Tablet:*** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).* – *Acute promyelocytic leukaemia*
tioguanine **[c]**	***Solid oral dosage form:*** *40 mg.* – *Acute lymphoblastic leukaemia*
vinblastine	***Injection:*** *10 mg/10 mL (sulfate) in vial.* ***Powder for injection:*** *10 mg (sulfate) in vial.* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Low-grade glioma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*
vincristine	***Injection:*** *1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.* ***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Follicular lymphoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Retinoblastoma* – *Rhabdomyosarcoma*
vinorelbine	***Capsule:*** *20 mg; 30 mg; 80 mg.* ***Injection:*** *10 mg/mL in 1 mL vial; 50 mg/5 mL in 5 mL vial.* – *Non-small cell lung cancer* – *Metastatic breast cancer* – *Rhabdomyosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.2 *Targeted therapies*

Complementary List

all-trans retinoid acid (ATRA)	***Capsule:*** *10 mg.* – *Acute promyelocytic leukaemia.*
bortezomib	***Powder for injection:*** *3.5 mg in vial.* – *Multiple myeloma*
dasatinib	***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
☐ *erlotinib* *Therapeutic alternatives:* – *afatinib* – *gefitinib*	***Tablet:*** *100 mg, 150 mg.* – *EGFR mutation-positive advanced non-small cell lung cancer*
everolimus	***Tablet:*** *2.5 mg; 5 mg; 7.5 mg; 10 mg.* ***Tablet (dispersible):*** *2 mg; 3 mg; 5 mg.* – *Subependymal giant cell astrocytoma*
ibrutinib	***Capsule:*** *140 mg.* – *Relapsed/refractory chronic lymphocytic leukaemia*
imatinib	***Solid oral dosage form:*** *100 mg; 400 mg.* – *Chronic myeloid leukaemia* – *Gastrointestinal stromal tumour* – *Philadelphia chromosome positive acute lymphoblastic leukaemia*
nilotinib	***Capsule:*** *150 mg; 200 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
*rituximab** * *including quality-assured biosimilars*	***Injection (intravenous):*** *100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.* – *Chronic lymphocytic leukaemia* – *Diffuse large B-cell lymphoma* – *Follicular lymphoma*
*trastuzumab** * *including quality-assured biosimilars*	***Powder for injection:*** *60 mg; 150 mg; 440 mg in vial.* – *Early stage HER2 positive breast cancer* – *Metastatic HER2 positive breast cancer*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.3 *Immunomodulators*

Complementary List

*filgrastim** * *including quality-assured biosimilars*	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.* ***Injection:*** *300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*
lenalidomide	***Capsule:*** *25 mg.* – *Multiple myeloma*
☐ *nivolumab** *Therapeutic alternatives**: – *pembrolizumab* * *including quality-assured biosimilars*	***Concentrate solution for infusion:*** *10 mg/mL.* – *Metastatic melanoma*
thalidomide	***Capsule:*** *50 mg.* – *Multiple myeloma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.4 *Hormones and antihormones*

Complementary List

☐ *abiraterone* *Therapeutic alternatives:* *– enzalutamide*	***Tablet:*** *250 mg; 500 mg.* *– Metastatic castration-resistant prostate cancer*
☐ *anastrozole* *Therapeutic alternatives:* *– 4th level ATC chemical subgroup (L02BG Aromatase inhibitors)*	***Tablet:*** *1 mg.* *– Early stage breast cancer* *– Metastatic breast cancer*
☐ *bicalutamide* *Therapeutic alternatives:* *– flutamide* *– nilutamide*	***Tablet:*** *50 mg.* *– Metastatic prostate cancer*
dexamethasone	***Injection:*** *4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.* ***Oral liquid:*** *2 mg/5 mL* [c]. ***Tablet:*** *2 mg* [c]; *4 mg.* *– Acute lymphoblastic leukaemia* *– Burkitt lymphoma* *– Multiple myeloma*
hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* *– Acute lymphoblastic leukaemia* *– Burkitt lymphoma*
☐ *leuprorelin* *Therapeutic alternatives:* *– goserelin* *– triptorelin*	***Injection:*** *7.5 mg; 22.5 mg in pre-filled syringe.* *– Early stage breast cancer* *– Metastatic prostate cancer.*
methylprednisolone [c]	***Injection:*** *40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.* *– Acute lymphoblastic leukamia* *– Burkitt lymphoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
☐ *prednisolone*	***Oral liquid:*** *5 mg/mL* *[c]*
Therapeutic alternatives: *– prednisone*	***Tablet:*** *5 mg; 25 mg.* *– Acute lymphoblastic leukaemia* *– Burkitt lymphoma* *– Chronic lymphocytic leukaemia* *– Diffuse large B-cell lymphoma* *– Follicular lymphoma* *– Hodgkin lymphoma* *– Metastatic castration-resitsant prostate cancer* *– Multiple myeloma*
tamoxifen	***Tablet:*** *10 mg; 20 mg (as citrate).* *– Early stage breast cancer* *– Metastatic breast cancer.*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.5 *Supportive medicines*

Complementary List

allopurinol ***[c]***	***Tablet:*** *100 mg; 300 mg.* – *Tumour lysis syndrome*
mesna	***Injection:*** *100 mg/mL in 4 mL and 10 mL ampoules.* ***Tablet:*** *400 mg; 600 mg.* – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Ovarian germ cell tumour* – *Osteosarcoma* – *Rhabdomyosarcoma* – *Testicular germ cell tumour*
rasburicase	***Powder and solvent for solution for infusion:*** *1.5 mg; 7.5 mg in vial.* – *Tumour lysis syndrome*
zoledronic acid	***Concentrate solution for infusion:*** *4 mg/5 mL in 5 mL vial.* ***Solution for infusion:*** *4 mg/100 mL in 100 mL bottle.* – *Malignancy-related bone disease*

9. ANTIPARKINSONISM MEDICINES

☐ biperiden Therapeutic alternatives: – trihexyphenidyl	**Injection:** 5 mg (lactate) in 1 mL ampoule. **Tablet:** 2 mg (hydrochloride).
levodopa + ☐ carbidopa Therapeutic alternatives: – benserazide (for carbidopa)	**Tablet:** 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.

10. MEDICINES AFFECTING THE BLOOD

10.1 Antianaemia medicines

ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/mL. **Tablet:** equivalent to 60 mg iron.
ferrous salt + folic acid	**Tablet:** equivalent to 60 mg iron + 400 micrograms folic acid. * nutritional supplement for use during pregnancy
folic acid	**Tablet:** 400 micrograms*; 1 mg; 5 mg. * periconceptual use for prevention of first occurrence of neural tube defects
hydroxocobalamin	**Injection:** 1 mg/mL (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.
Complementary List	
☐ *erythropoiesis-stimulating agents** *Therapeutic alternatives:* – *epoetin alfa, beta and theta* – *darbepoetin alfa* – *methoxy polyethylene glycol-epoetin beta* * *including quality-assured biosimilars*	***Injection:*** *pre-filled syringe* *1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.*

10. MEDICINES AFFECTING THE BLOOD *(continued)*

10.2 Medicines affecting coagulation

☐ dabigatran Therapeutic alternatives: – apixaban – edoxaban – rivaroxaban	**Capsule:** 110 mg; 150 mg.
☐ enoxaparin* Therapeutic alternatives*: – dalteparin – nadroparin * *including quality-assured biosimilars*	**Injection:** ampoule or pre-filled syringe 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.
heparin sodium	**Injection:** 1000 IU/mL; 5000 IU/mL; 20 000 IU/mL in 1 mL ampoule.
phytomenadione	**Injection:** 1 mg/mL [c]; 10 mg/mL in ampoule. **Tablet:** 10 mg.
protamine sulfate	**Injection:** 10 mg/mL in 5 mL ampoule.
tranexamic acid	**Injection:** 100 mg/mL in 10 mL ampoule.
☐ warfarin Therapeutic alternatives to be reviewed (2023)	**Tablet:** 1 mg; 2 mg; 5 mg (sodium).
Complementary List	
desmopressin [c]	***Injection:*** *4 micrograms/mL (as acetate) in 1 mL ampoule.* ***Nasal spray:*** *10 micrograms (as acetate) per dose.*
heparin sodium [c]	***Injection:*** *1000 IU/mL; 5000 IU/mL in 1 mL ampoule.*
protamine sulfate [c]	***Injection:*** *10 mg/mL in 5 mL ampoule.*
☐ *warfarin* [c] *Therapeutic alternatives to be reviewed (2023)*	***Tablet:*** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium).*

10.3 Other medicines for haemoglobinopathies

Complementary List	
☐ *deferoxamine* *Therapeutic alternatives:* – *deferasirox (oral)*	***Powder for injection:*** *500 mg (mesilate) in vial.*
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 500 mg; 1 g.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh-frozen plasma

platelets

red blood cells

whole blood

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11.2.1 *Human immunoglobulins*

anti-D immunoglobulin	**Injection:** 250 micrograms in single-dose vial.
anti-rabies immunoglobulin	**Injection:** 150 IU/mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	
normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.** ***Intravenous administration:*** *5%; 10% protein solution.*** ***Subcutaneous administration:*** *15%; 16% protein solution.** * *Indicated for primary immune deficiency.* ** *Indicated for primary immune deficiency and Kawasaki disease.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES *(continued)*	
11.2.2 ***Blood coagulation factors***	
Complementary List	
☐ *coagulation factor VIII* *Therapeutic alternatives to be reviewed (2023)*	***Powder for injection:*** *500 IU/vial.*
☐ *coagulation factor IX* *Therapeutic alternatives to be reviewed (2023)*	***Powder for injection:*** *500 IU/vial; 1000 IU/vial.*
11.3 Plasma substitutes	
☐ dextran 70 Therapeutic alternatives: – Polygeline injectable solution 3.5%	**Injectable solution:** 6%.

12. CARDIOVASCULAR MEDICINES

12.1 Antianginal medicines

☐ bisoprolol	**Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives: – carvedilol – metoprolol	
glyceryl trinitrate	**Tablet (sublingual):** 500 micrograms.
isosorbide dinitrate	**Tablet (sublingual):** 5 mg.
verapamil	**Tablet:** 40 mg; 80 mg (hydrochloride).

12.2 Antiarrhythmic medicines

☐ bisoprolol	**Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives: – carvedilol – metoprolol	
digoxin	**Injection:** 250 micrograms/mL in 2 mL ampoule. **Oral liquid:** 50 micrograms/mL. **Tablet:** 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	**Injection:** 100 micrograms/mL (as acid tartrate or hydrochloride) in 10 mL ampoule.
lidocaine	**Injection:** 20 mg/mL (hydrochloride) in 5 mL ampoule.
verapamil	**Injection:** 2.5 mg/mL (hydrochloride) in 2 mL ampoule. **Tablet:** 40 mg; 80 mg (hydrochloride).
Complementary List	
amiodarone	***Injection:*** *50 mg/mL (hydrochloride) in 3 mL ampoule.* ***Tablet:*** *100 mg; 200 mg; 400 mg (hydrochloride).*

12. CARDIOVASCULAR MEDICINES *(continued)*

12.3 Antihypertensive medicines

☐ amlodipine Therapeutic alternatives: – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives)	**Tablet:** 5 mg (as maleate, mesylate or besylate).
☐ bisoprolol Therapeutic alternatives: – atenolol* – carvedilol – metoprolol	**Tablet:** 1.25 mg; 5 mg. * atenolol should not be used as a first-line agent in uncomplicated hypertension in patients > 60 years.
☐ enalapril Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).
hydralazine*	**Powder for injection:** 20 mg (hydrochloride) in ampoule. **Tablet:** 25 mg; 50 mg (hydrochloride). * Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
☐ hydrochlorothiazide Therapeutic alternatives: – chlorothiazide – chlorthalidone – indapamide	**Oral liquid:** 50 mg/5 mL. **Solid oral dosage form:** 12.5 mg; 25 mg.
☐ lisinopril + ☐ amlodipine Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	**Tablet:** 10 mg + 5 mg; 20 mg + 5 mg; 20 mg + 10 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*	
☐ lisinopril + ☐ hydrochlorothiazide Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril) – chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	**Tablet:** 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg.
☐ losartan Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	**Tablet:** 25 mg; 50 mg; 100 mg.
methyldopa*	**Tablet:** 250 mg. * Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
☐ telmisartan + ☐ amlodipine Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	**Tablet:** 40 mg + 5 mg; 80 mg + 5 mg; 80 mg + 10 mg.
☐ telmisartan + ☐ hydrochlorothiazide Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan) – chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	**Tablet:** 40 mg + 12.5 mg; 80 mg + 12.5 mg; 80 mg + 25 mg.
Complementary List	
sodium nitroprusside	***Powder for infusion:*** *50 mg in ampoule.*

12. CARDIOVASCULAR MEDICINES *(continued)*	
12.4 Medicines used in heart failure	
☐ bisoprolol Therapeutic alternatives: – carvedilol – metoprolol	**Tablet:** 1.25 mg; 5 mg.
digoxin	**Injection:** 250 micrograms/mL in 2 mL ampoule. **Oral liquid:** 50 micrograms/mL. **Tablet:** 62.5 micrograms; 250 micrograms.
☐ enalapril Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).
☐ furosemide Therapeutic alternatives: – bumetanide – torasemide	**Injection:** 10 mg/mL in 2 mL ampoule. **Oral liquid:** 20 mg/5 mL [c]. **Tablet:** 40 mg.
☐ hydrochlorothiazide Therapeutic alternatives: – chlorothiazide – chlorthalidone – indapamide	**Oral liquid:** 50 mg/5 mL. **Solid oral dosage form:** 25 mg.
☐ losartan Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	**Tablet:** 25 mg; 50 mg; 100 mg.
spironolactone	**Tablet:** 25 mg.
Complementary List	
dopamine	***Injection:*** *40 mg/mL (hydrochloride) in 5 mL vial.*

12. CARDIOVASCULAR MEDICINES *(continued)*

12.5 Antithrombotic medicines

12.5.1 *Anti-platelet medicines*

acetylsalicylic acid	**Tablet:** 100 mg.
clopidogrel	**Tablet:** 75 mg; 300 mg.

12.5.2 *Thrombolytic medicines*

Complementary List

alteplase	***Powder for injection:*** *10 mg; 20 mg; 50 mg in vial*
streptokinase	***Powder for injection:*** *1.5 million IU in vial.*

12.6 Lipid-lowering agents

☐ simvastatin*	**Tablet:** 5 mg; 10 mg; 20 mg; 40 mg.
Therapeutic alternatives: – atorvastatin – fluvastatin – lovastatin – pravastatin	* For use in high-risk patients.

13. DERMATOLOGICAL MEDICINES (topical)

13.1 Antifungal medicines

☐ miconazole Therapeutic alternatives: – 4th level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	**Cream or ointment:** 2% (nitrate).
selenium sulfide	**Detergent-based suspension:** 2%.
sodium thiosulfate	**Solution:** 15%.
terbinafine	**Cream or ointment:** 1% (hydrochloride).

13.2 Anti-infective medicines

mupirocin	**Cream:** 2% (as calcium). **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] > 2 months.

13.3 Anti-inflammatory and antipruritic medicines

☐ betamethasone [a] Therapeutic alternatives: – 4th level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
calamine	**Lotion.**
☐ hydrocortisone Therapeutic alternatives: – 4th level ATC chemical subgroup (D07AA Corticosteroids, weak (group I))	**Cream or ointment:** 1% (acetate).

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*	
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	**Cream or lotion:** 5%.
☐ calcipotriol Therapeutic alternatives: – calcitriol – tacalcitol	**Cream or ointment:** 50 micrograms/mL (0.005%). **Lotion:** 50 micrograms/mL (0.005%).
coal tar	**Solution:** 5%.
fluorouracil	**Ointment:** 5%.
☐ podophyllum resin Therapeutic alternatives: – podophyllotoxin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.
urea	**Cream or ointment:** 5%; 10%.
13.5 Scabicides and pediculicides	
☐ benzyl benzoate [a] Therapeutic alternatives: – precipitated sulfur topical ointment	**Lotion:** 25%. [a] > 2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.

14. DIAGNOSTIC AGENTS

14.1 Ophthalmic medicines

fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide Therapeutic alternatives: – atropine – cyclopentolate	**Eye drops:** 0.5%.

14.2 Radiocontrast media

☐ amidotrizoate Therapeutic alternatives to be reviewed (2023)	**Injection:** 140 mg to 420 mg iodine/mL (as sodium or meglumine salt) in 20 mL ampoule.
barium sulfate	**Aqueous suspension.**
☐ iohexol Therapeutic alternatives to be reviewed (2023)	**Injection:** 140 mg to 350 mg iodine/mL in 5 mL; 10 mL; 20 mL ampoules.
Complementary List	
barium sulfate [c]	***Aqueous suspension.***
☐ *meglumine iotroxate* *Therapeutic alternatives to be reviewed (2023)*	***Solution:*** *5 g to 8 g iodine in 100 mL to 250 mL.*

15. ANTISEPTICS AND DISINFECTANTS

15.1 Antiseptics

☐ chlorhexidine Therapeutic alternatives to be reviewed (2023)	**Solution:** 5% (digluconate).
☐ ethanol Therapeutic alternatives: – propanol	**Solution:** 70% (denatured).
☐ povidone iodine Therapeutic alternatives: – iodine	**Solution:** 10% (equivalent to 1% available iodine).

15.2 Disinfectants

alcohol based hand rub	**Solution:** containing ethanol 80% volume/volume. **Solution:** containing isopropyl alcohol 75% volume/volume.
chlorine base compound	**Liquid:** (0.1% available chlorine) for solution. **Powder:** (0.1% available chlorine) for solution. **Solid:** (0.1% available chlorine) for solution.
☐ chloroxylenol Therapeutic alternatives: – 4th level ATC chemical subgroup (D08AE Phenol and derivatives)	**Solution:** 4.8%.
glutaral	**Solution:** 2%.

16. DIURETICS	
amiloride	**Tablet:** 5 mg (hydrochloride).
☐ furosemide Therapeutic alternatives: – bumetanide – torasemide	**Injection:** 10 mg/mL in 2 mL ampoule. **Oral liquid:** 20 mg/5 mL [c]. **Tablet:** 10 mg [c]; 20 mg [c]; 40 mg.
☐ hydrochlorothiazide Therapeutic alternatives: – chlorothiazide – chlortalidone – indapamide	**Solid oral dosage form:** 25 mg.
mannitol	**Injectable solution:** 10%; 20%.
spironolactone	**Tablet:** 25 mg.
Complementary List	
☐ *hydrochlorothiazide* [c] *Therapeutic alternatives:* – *chlorothiazide* – *chlortalidone*	***Tablet (scored):** 25 mg.*
mannitol [c]	***Injectable solution:** 10%; 20%.*
spironolactone [c]	***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.* ***Tablet:** 25 mg.*

17. GASTROINTESTINAL MEDICINES

Complementary List

pancreatic enzymes [c]	*Age-appropriate formulations and doses including lipase, protease and amylase.*

17.1 Antiulcer medicines

☐ omeprazole Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	**Powder for injection:** 40 mg in vial **Powder for oral liquid:** 20 mg; 40 mg sachets. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
☐ ranitidine Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BA H2-receptor antagonists) excluding combinations	**Injection:** 25 mg/mL (as hydrochloride) in 2 mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL. **Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide [a]	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL [c]. **Tablet:** 10 mg (hydrochloride). [a] Not in neonates.
☐ ondansetron [a] Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg base/mL in 2 mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base; Eq 24 mg base. [a] > 1 month.

Complementary list

aprepitant	***Capsule:*** *80 mg; 125 mg; 165 mg.* ***Powder for oral suspension:*** *125 mg in sachet.*

17. GASTROINTESTINAL MEDICINES *(continued)*

17.3 Anti-inflammatory medicines

☐ sulfasalazine	**Retention enema.**
Therapeutic alternatives: – mesalazine	**Suppository:** 500 mg. **Tablet:** 500 mg.
Complementary List	
hydrocortisone	***Retention enema:** 100 mg/60 mL.* ***Suppository:** 25 mg (acetate).*
prednisolone	***Retention enema:** 20 mg/100 mL (as sodium phosphate).*

17.4 Laxatives

☐ senna	**Tablet:** 7.5 mg (sennosides) (or traditional dosage forms).
Therapeutic alternatives: – bisacodyl	

17.5 Medicines used in diarrhoea

oral rehydration salts – zinc sulfate [c]	**Co-package containing:** **ORS powder for dilution** (see Section 17.5.1) – zinc sulfate **solid oral dosage form** 20 mg (see Section 17.5.2)

17.5.1 *Oral rehydration*

oral rehydration salts — **Powder for dilution** in 200 mL; 500 mL; 1 L.

glucose:	75 mEq
sodium:	75 mEq or mmol/L
chloride:	65 mEq or mmol/L
potassium:	20 mEq or mmol/L
citrate:	10 mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

* trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

17.5.2 *Medicines for diarrhoea*

zinc sulfate* — **Solid oral dosage form:** 20 mg.

* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

18. MEDICINES FOR ENDOCRINE DISORDERS	
18.1 Adrenal hormones and synthetic substitutes	
fludrocortisone	**Tablet:** 100 micrograms (acetate).
hydrocortisone	**Tablet:** 5 mg; 10 mg; 20 mg.
18.2 Androgens	
Complementary List	
testosterone	***Injection:*** *200 mg (enanthate) in 1 mL ampoule.*
18.3 Estrogens	
18.4 Progestogens	
☐ medroxyprogesterone acetate Therapeutic alternatives: – norethisterone	**Tablet:** 5 mg.
18.5 Medicines for diabetes	
18.5.1 ***Insulins***	
insulin injection (soluble)* * *including quality-assured biosimilars*	**Injection:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial.
intermediate-acting insulin* * *including quality-assured biosimilars*	**Injection:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial (as compound insulin zinc suspension or isophane insulin).
☐ long-acting insulin analogues* Therapeutic alternatives: – insulin degludec – insulin detemir – insulin glargine * *including quality-assured biosimilars*	**Injection:** 100 IU/mL in 3 mL cartridge or pre-filled pen.

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*	
18.5.2 *Oral hypoglycaemic agents*	
☐ empagliflozin Therapeutic alternatives: – canagliflozin – dapagliflozin	**Tablet:** 10 mg; 25 mg.
☐ gliclazide* Therapeutic alternatives: – 4th level ATC chemical subgroup (A10BB Sulfonylureas)	**Solid oral dosage form:** (controlled-release tablets) 30 mg; 60 mg; 80 mg. * glibenclamide not suitable above 60 years.
metformin	**Tablet:** 500 mg (hydrochloride).
Complementary List	
metformin ***[c]***	***Tablet:*** *500 mg (hydrochloride).*
18.6 Medicines for hypoglycaemia	
glucagon	**Injection:** 1 mg/mL.
Complementary List	
diazoxide ***[c]***	***Oral liquid:*** *50 mg/mL.* ***Tablet:*** *50 mg.*
18.7 Thyroid hormones and antithyroid medicines	
levothyroxine	**Tablet:** 25 micrograms **[c]**; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	**Tablet:** 60 mg.
☐ methimazole Therapeutic alternatives: – carbimazole (depending on local availability)	**Tablet:** 5mg, 10mg, 20mg.
propylthiouracil*	**Tablet:** 50 mg. * For use when alternative first-line treatment is not appropriate or available; and in patients during the first trimester of pregnancy.

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

Complementary List

Lugol's solution [c]	***Oral liquid:*** *about 130 mg total iodine/mL.*
☐ *methimazole* [c] *Therapeutic alternatives:* – *carbimazole (depending on local availability)*	***Tablet:*** *5mg, 10mg, 20mg.*
potassium iodide [c]	***Tablet:*** *60 mg.*
*propylthiouracil** [c]	***Tablet:*** *50 mg.* * *For use when alternative first-line treatment is not appropriate or available.*

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	**Injection.**

19.2 Sera, immunoglobulins and monoclonal antibodies

All plasma fractions should comply with the WHO requirements.

anti-rabies virus monoclonal antibodies* * *including quality-assured biosimilars*	**Injection:** 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human). **Injection:** 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
antivenom immunoglobulin*	**Injection.** * Exact type to be defined locally.
diphtheria antitoxin	**Injection:** 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	**Injection:** 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial.

19. IMMUNOLOGICALS *(continued)*

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers based on recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at September 2020. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

Recommendations for all

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

human papilloma virus (HPV) vaccine

measles vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

19. IMMUNOLOGICALS *(continued)*
Recommendations for certain regions
Japanese encephalitis vaccine
tick-borne encephalitis vaccine
yellow fever vaccine
Recommendations for some high-risk populations
cholera vaccine
dengue vaccine
hepatitis A vaccine
meningococcal meningitis vaccine
rabies vaccine
typhoid vaccine
Recommendations for immunization programmes with certain characteristics
influenza vaccine (seasonal)
mumps vaccine
varicella vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
☐ atracurium Therapeutic alternatives to be reviewed (2023)	**Injection:** 10 mg/mL (besylate).
neostigmine	**Injection:** 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg/mL (chloride) in 2 mL ampoule. **Powder for injection:** (chloride), in vial.
☐ vecuronium [C] Therapeutic alternatives to be reviewed (2023)	**Powder for injection:** 10 mg (bromide) in vial.
Complementary List	
pyridostigmine	***Injection:*** *1 mg in 1 mL ampoule.* ***Tablet:*** *60 mg (bromide).*
☐ *vecuronium* *Therapeutic alternatives to be reviewed (2023)*	***Powder for injection:*** *10 mg (bromide) in vial.*

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% w/w.
azithromycin	**Solution (eye drops):** 1.5%. – *Trachoma*
erythromycin	**Ointment:** 0.5% [c]. – *Infections due to Chlamydia trachomatis or Neisseria gonorrhoea*
☐ gentamicin Therapeutic alternatives: – amikacin – kanamycin – netilmicin – tobramycin	**Solution (eye drops):** 0.3% (sulfate). – *Bacterial blepharitis* – *Bacterial conjunctivitis*
natamycin	**Suspension (eye drops):** 5% – *Fungal keratitis*
☐ ofloxacin Therapeutic alternatives: – 4th level ATC chemical subgroup (S01AE Fluoroquinolones)	**Solution (eye drops):** 0.3%. – *Bacterial conjunctivitis* – *Bacterial keratitis*
☐ tetracycline Therapeutic alternatives: – chlortetracycline – oxytetracycline	**Eye ointment:** 1% (hydrochloride). – *Bacterial blepharitis* – *Bacterial conjunctivitis* – *Bacterial keratitis* – *Trachoma*

21.2 Anti-inflammatory agents

☐ prednisolone Therapeutic alternatives to be reviewed (2023)	**Solution (eye drops):** 0.5% (sodium phosphate).

21.3 Local anaesthetics

☐ tetracaine [a] Therapeutic alternatives: – 4th level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	**Solution (eye drops):** 0.5% (hydrochloride). [a] Not in preterm neonates.

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*

21.5 Mydriatics

☐ atropine [a]	**Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate).
Therapeutic alternatives*: – cyclopentolate hydrochloride – homatropine hydrobromide	[a] > 3 months.
* *EMLc only*	

Complementary List

epinephrine (adrenaline)	***Solution (eye drops):*** *2% (as hydrochloride).*

21.6 Anti-vascular endothelial growth factor (VEGF) preparations

Complementary List

*bevacizumab**	***Injection:*** *25 mg/mL.*
* *including quality-assured biosimilars*	

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

22.1 Contraceptives

22.1.1 *Oral hormonal contraceptives*

☐ ethinylestradiol + ☐ levonorgestrel Therapeutic alternatives to be reviewed (2023)	**Tablet:** 30 micrograms + 150 micrograms.
☐ ethinylestradiol + ☐ norethisterone Therapeutic alternatives to be reviewed (2023)	**Tablet:** 35 micrograms + 1 mg.
levonorgestrel	**Tablet:** 30 micrograms; 750 micrograms (pack of two); 1.5 mg.
ulipristal	**Tablet:** 30 mg (as acetate)

22.1.2 *Injectable hormonal contraceptives*

estradiol cypionate + medroxyprogesterone acetate	**Injection:** 5 mg + 25 mg.
medroxyprogesterone acetate	**Injection (intramuscular):** 150 mg mL in 1 mL vial. **Injection (subcutaneous):** 104 mg/0.65 mL in pre-filled syringe or single-dose injection delivery system.
norethisterone enantate	**Oily solution:** 200 mg/mL in 1 mL ampoule.

22.1.3 *Intrauterine devices*

copper-containing device	
levonorgestrel-releasing intrauterine system	**Intrauterine system:** with reservoir containing 52 mg of levonorestrel

22.1.4 *Barrier methods*

condoms

diaphragms

22.1.5 *Implantable contraceptives*

etonogestrel-releasing implant	**Single-rod etonogestrel-releasing implant:** containing 68 mg of etonogestrel.
levonorgestrel-releasing implant	**Two-rod levonorgestrel-releasing implant:** each rod containing 75 mg of levonorgestrel (150 mg total).

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*	
22.1.6 ***Intravaginal contraceptives***	
ethinylestradiol + etonogestrel	**Vaginal ring:** containing 2.7 mg + 11.7 mg
progesterone vaginal ring*	**Progesterone-releasing vaginal ring:** containing 2.074 g of micronized progesterone. * For use in women actively breastfeeding at least 4 times per day.
22.2 Ovulation inducers	
Complementary List	
clomifene	***Tablet:*** *50 mg (citrate).*
22.3 Uterotonics	
carbetocin	**Injection (heat stable):** 100 micrograms/mL
☐ ergometrine Therapeutic alternatives: – methylergometrine	**Injection:** 200 micrograms (hydrogen maleate) in 1 mL ampoule.
mifepristone – misoprostol Where permitted under national law and where culturally acceptable.	**Tablet** 200 mg – **tablet** 200 micrograms. **Co-package containing:** mifepristone 200 mg tablet [1] and misoprostol 200 micrograms tablet [4]
misoprostol	**Tablet:** 200 micrograms. – Management of incomplete abortion and miscarriage; – Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used **Vaginal tablet:** 25 micrograms.* * Only for use for induction of labour where appropriate facilities are available.
oxytocin	**Injection:** 10 IU in 1 mL.
22.4 Antioxytocics (tocolytics)	
nifedipine	**Immediate-release capsule:** 10 mg.

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

22.5 Other medicines administered to the mother

dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.	
multiple micronutrient supplement*	**Tablet containing:**	
	Vitamin A (retinol acetate)	800 micrograms retinol activity equivalent
	Vitamin C (ascorbic acid)	70 mg
	Vitamin D (cholecalciferol)	5 micrograms (200 IU)
	Vitamin E (alpha tocopherol succinate)	10 mg alpha tocopherol equivalent
	Vitamin B1 (thiamine mononitrate)	1.4 mg
	Vitamin B2 (riboflavin)	1.4 mg
	Vitamin B3 (niacinamide)	18 mg niacin equivalent
	Vitamin B6 (pyridoxine hydrochloride)	1.9 mg
	Folic acid (folic acid)	680 micrograms dietary folate equivalent (400 micrograms)
	Vitamin B12 (cyanocobalamin)	2.6 micrograms
	Iron (ferrous fumarate)	30 mg
	Iodine (potassium iodide)	150 micrograms
	Zinc (zinc oxide)	15 mg
	Selenium (sodium selenite)	65 micrograms
	Copper (cupric oxide)	2 mg
	* For use in specific contexts. Refer to current WHO recommendations.	
tranexamic acid	**Injection:** 100 mg/mL in 10 mL ampoule	

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*	
22.6 Medicines administered to the neonate [c]	
caffeine citrate [c]	**Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL). **Oral liquid:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine [c]	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).
Complementary List	
☐ *ibuprofen [c]* *Therapeutic alternatives:* *– indometacin*	***Solution for injection:*** *5 mg/mL.*
☐ *prostaglandin E1 [c]* *Therapeutic alternatives:* *– prostaglandin E2*	***Solution for injection:*** *0.5 mg/mL in alcohol.*
surfactant [c]	***Suspension for intratracheal instillation:*** *25 mg/mL or 80 mg/mL.*
23. PERITONEAL DIALYSIS SOLUTION	
Complementary List	
intraperitoneal dialysis solution (of appropriate composition)	***Parenteral solution.***

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines used in psychotic disorders

☐ chlorpromazine Therapeutic alternatives to be reviewed (2023)	**Injection:** 25 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 25 mg/5 mL (hydrochloride). **Tablet:** 100 mg (hydrochloride).
☐ fluphenazine Therapeutic alternatives to be reviewed (2023)	**Injection:** 25 mg (decanoate or enantate) in 1 mL ampoule.
☐ haloperidol Therapeutic alternatives to be reviewed (2023)	**Injection:** 5 mg in 1 mL ampoule. **Tablet:** 2 mg; 5 mg.
☐ paliperidone Therapeutic alternatives: – risperidone injection	**Injection (prolonged-release):** 25 mg; 50 mg; 75 mg; 100 mg; 150 mg (as palmitate) in pre-filled syringe
risperidone	**Solid oral dosage form:** 0.25 mg to 6.0 mg.
Complementary List	
chlorpromazine [c]	***Injection:*** *25 mg/mL (hydrochloride) in 2 mL ampoule.* ***Oral liquid:*** *25 mg/5 mL (hydrochloride).* ***Tablet:*** *10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).*
clozapine	***Solid oral dosage form:*** *25 to 200 mg.*
haloperidol [c]	***Injection:*** *5 mg in 1 mL ampoule.* ***Oral liquid:*** *2 mg/mL.* ***Solid oral dosage form:*** *0.5 mg; 2 mg; 5 mg.*

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

24.2 Medicines used in mood disorders

24.2.1 *Medicines used in depressive disorders*

☐ amitriptyline Therapeutic alternatives to be reviewed (2023)	**Tablet:** 25 mg; 75mg (hydrochloride).
☐ fluoxetine Therapeutic alternatives: – citalopram – escitalopram – fluvoxamine – paroxetine – sertraline	**Solid oral dosage form:** 20 mg (as hydrochloride).
Complementary List	
fluoxetine [a] *[c]*	***Solid oral dosage form:*** *20 mg (as hydrochloride).* [a] > 8 years.

24.2.2 *Medicines used in bipolar disorders*

carbamazepine	**Tablet (scored):** 100 mg; 200 mg.
lithium carbonate	**Solid oral dosage form:** 300 mg.
valproic acid (sodium valproate)* * *avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*	**Tablet (enteric-coated):** 200 mg; 500 mg.

24.3 Medicines for anxiety disorders

☐ diazepam Therapeutic alternatives to be reviewed (2023)	**Tablet (scored):** 2 mg; 5 mg.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*	
24.4 Medicines used for obsessive compulsive disorders	
clomipramine	**Capsule:** 10 mg; 25 mg (hydrochloride).
24.5 Medicines for disorders due to psychoactive substance use	
bupropion	**Tablet (sustained-release):** 150 mg (hydrochloride)
nicotine replacement therapy (NRT)	**Chewing gum:** 2 mg; 4 mg (as polacrilex). **Transdermal patch:** 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
varenicline	**Tablet:** 0.5 mg; 1 mg.
Complementary List	
☐ *methadone** *Therapeutic alternatives:* *– buprenorphine*	***Concentrate for oral liquid:*** *5 mg/mL; 10 mg/mL (hydrochloride).* ***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL (hydrochloride).* * *The medicines should only be used within an established support programme.*

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines and medicines for chronic obstructive pulmonary disease

☐ budesonide Therapeutic alternatives: – beclometasone – ciclesonide – flunisolide – fluticasone – mometasone	**Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose.
☐ budesonide + ☐ formoterol Therapeutic alternatives: – beclometasone + formoterol – budesonide + salmeterol – fluticasone + formoterol – fluticasone furoate + vilanterol – mometasone + formoterol	**Dry powder inhaler:** 100 micrograms + 6 micrograms per dose; 200 micrograms + 6 micrograms per dose
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
ipratropium bromide	**Inhalation (aerosol):** 20 micrograms/metered dose.
☐ salbutamol Therapeutic alternatives: – terbutaline	**Inhalation (aerosol):** 100 micrograms (as sulfate) per dose. **Injection:** 50 micrograms/mL (as sulfate) in 5 mL ampoule. **Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose. **Respirator solution for use in nebulizers:** 5 mg/mL (as sulfate).
☐ tiotropium Therapeutic alternatives: – aclidinium – glycopyrronium – umeclidinium	**Powder for inhalaton, capsule:** 18 micrograms **Inhalation solution:** 1.25 micrograms; 2.5 micrograms per actuation

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**

26.2 Parenteral

glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 4% glucose, 0.18% sodium chloride (equivalent to Na+ 30 mmol/L, Cl- 30 mmol/L). **Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L) [c] .
potassium chloride	**Solution:** 11.2% in 20 mL ampoule (equivalent to K+ 1.5 mmol/mL, Cl- 1.5 mmol/mL). **Solution for dilution:** 7.5% (equivalent to K 1 mmol/mL and Cl 1 mmol/mL) [c] ; 15% (equivalent to K 2 mmol/mL and Cl 2 mmol/mL) [c] .
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+ 167 mmol/L, HCO3- 167 mmol/L). **Solution:** 8.4% in 10 mL ampoule (equivalent to Na+ 1000 mmol/L, HCO3-1000 mmol/L).
sodium lactate, compound solution	**Injectable solution.**

26.3 Miscellaneous

water for injection	2 mL; 5 mL; 10 mL ampoules.

27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.
calcium	**Tablet:** 500 mg (elemental).
☐ colecalciferol [c] Therapeutic alternatives: – ergocalciferol	**Oral liquid:** 400 IU/mL. **Solid oral dosage form:** 400 IU; 1000 IU.
☐ ergocalciferol Therapeutic alternatives: – colecalciferol	**Oral liquid:** 250 micrograms/mL (10 000 IU/mL). **Solid oral dosage form:** 1.25 mg (50 000 IU).
iodine	**Capsule:** 190 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
multiple micronutrient powder [c]	**Sachets containing:** – iron (elemental) 12.5 mg (as coated ferrous fumarate) – zinc (elemental) 5 mg – vitamin A 300 micrograms – with or without other micronutrients at recommended daily values
nicotinamide	**Tablet:** 50 mg.
pyridoxine	**Tablet:** 25 mg (hydrochloride).
retinol	**Capsule:** 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). **Oral oily solution:** 100 000 IU/mL (as palmitate) in multidose dispenser. **Tablet (sugar-coated):** 10 000 IU (as palmitate). **Water-miscible injection:** 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	**Tablet:** 5 mg.
thiamine	**Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:** 100 mg/mL in 10 mL ampoule.*

28. EAR, NOSE AND THROAT MEDICINES

acetic acid [c]	**Topical:** 2%, in alcohol.
☐ budesonide [c] Therapeutic alternatives to be reviewed (2023)	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin [c] Therapeutic alternatives: – ofloxacin	**Solution (ear drops):** 0.3% (as hydrochloride).
☐ xylometazoline [a] [c] Therapeutic alternatives to be reviewed (2023)	**Nasal spray:** 0.05%. [a] Not in children less than 3 months.

29. MEDICINES FOR DISEASES OF JOINTS

29.1 Medicines used to treat gout

allopurinol	**Tablet:** 100 mg.

29.2 Disease-modifying anti-rheumatic drugs (DMARDs)

chloroquine	**Tablet:** 100 mg; 150 mg (as phosphate or sulfate).
Complementary List	
azathioprine	***Tablet:*** *50 mg.*
hydroxychloroquine	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium salt).*
penicillamine	***Solid oral dosage form:*** *250 mg.*
sulfasalazine	***Tablet:*** *500 mg.*

29.3 Juvenile joint diseases

Complementary List	
*acetylsalicylic acid** *(acute or chronic use)*	***Suppository:*** *50 mg to 150 mg.* ***Tablet:*** *100 mg to 500 mg.* ** For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*

30. DENTAL PREPARATIONS	
fluoride	**Paste, cream or gel:** containing between 1000 and 1500 ppm fluoride (any type). **In other appropriate topical formulations.**
glass ionomer cement	**Single-use capsules:** 0.4 g powder + 0.09 mL liquid. **Multi-use bottle:** powder + liquid. Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
silver diamine fluoride	**Solution:** 38% w/v.

Table 1.1: Medicines with age or weight restrictions

artesunate + pyronaridine tetraphosphate	> 5 kg
atropine	> 3 months
bedaquiline	≥ 5 years
benzyl benzoate	> 2 years
betamethasone topical preparations	hydrocortisone preferred in neonates
cefazolin	> 1 month
ceftriaxone	> 41 weeks corrected gestational age
darunavir	> 3 years
delamanid	≥ 3 years (25 mg dispersible tablet) ≥ 6 years (50 mg tablet)
dihydroartemisinin + piperaquine phosphate	> 5 kg
diloxanide	> 25 kg
dolutegravir	≥ 4 weeks and ≥ 3 kg (10 mg dispersible tablet) ≥ 25 kg (50 mg tablet)
doxycycline	> 8 years (except for serious infections e.g. cholera)
fluoxetine	> 8 years
ibuprofen	> 3 months (except IV form for patent ductus arteriosus)
mefloquine	> 5 kg or > 3 months
metoclopramide	Not in neonates
nevirapine	> 6 weeks
ondansetron	> 1 month
silver sulfadiazine	> 2 months
tetracaine	Not in preterm neonates
xylometazoline	> 3 months

Table 1.2: Explanation of dosage forms

A. Principal dosage forms used in EML – oral administration

Term	Definition
Solid oral dosage form	Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability. The term 'solid oral dosage form' is never intended to allow any type of modified-release tablet.
Tablets	Refers to: • uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole; • unscored and scored*; • tablets that are intended to be chewed before being swallowed; • tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed; • tablets that are intended to be crushed before being swallowed. The term 'tablet' without qualification is never intended to allow any type of modified-release tablet. * Scored tablets may be divided for ease of swallowing, provided that dose is a whole number of tablets
Tablets (qualified)	Refers to a specific type of tablet: **chewable** - tablets that are intended to be chewed before being swallowed; **dispersible** - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed; **soluble** - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed; **crushable** - tablets that are intended to be crushed before being swallowed; **scored** - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet; **sublingual** - tablets that are intended to be placed beneath the tongue.

Table 1.2 *continued*

Term	Definition
	The term 'tablet' is *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Capsules	Refers to hard or soft capsules. The term 'capsule' without qualification is *never* intended to allow any type of modified-release capsule.
Capsules (qualified)	The term 'capsule' with qualification refers to **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Granules	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid. The term 'granules' without further qualification is *never* intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be *swallowed* i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but not those preparations intended for *oromucosal administration* e.g. gargles and mouthwashes. Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

B. Principal dosage forms used in EML – parenteral administration

Term	Definition
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term 'injection' is qualified by '(oily)' in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, pressurized inhalation, nebulizer.

Annex 2

WHO Model List of Essential Medicines for Children – 8th List (2021)

Explanatory notes

This Model List is intended for use for children up to and including 12 years of age

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost–effectiveness in a variety of settings.

The **square box symbol** (☐) is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the Anatomical Therapeutic Chemical (ATC) classification, which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The format and numbering of the 22nd WHO Model List of Essential Medicines is used for the 8th WHO Model Essential List for Children. Some sections have been deleted because they contain medicines that are not relevant for children.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List for Children carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance.

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 *Inhalational medicines*

halothane	**Inhalation.**
isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medical gas).

1.1.2 *Injectable medicines*

ketamine	**Injection:** 50 mg/mL (as hydrochloride) in 10 mL vial.
☐ propofol* Therapeutic alternatives: – thiopental	**Injection:** 10 mg/mL; 20 mg/mL.

1.2 Local anaesthetics

☐ bupivacaine Therapeutic alternatives to be reviewed (2023)	**Injection:** 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine Therapeutic alternatives to be reviewed (2023)	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.

1.3 Preoperative medication and sedation for short-term procedures

atropine	**Injection:** 1 mg (sulfate) in 1mL ampoule.
☐ midazolam Therapeutic alternatives to be reviewed (2023)	**Injection:** 1 mg/mL. **Oral liquid:** 2 mg/mL. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection**: 10 mg (sulfate or hydrochloride) in 1mL ampoule.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*

1.4 Medical gases

oxygen*	**Inhalation** For use in the management of hypoxaemia. * No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

ibuprofen [a]	**Oral liquid:** 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol*	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Suppository:** 100 mg. **Tablet:** 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2.2 Opioid analgesics

☐ morphine Therapeutic alternatives: – hydrormorphone – oxycodone	**Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. **Oral liquid:** 10 mg/5 mL (morphine hydrochloride or morphine sulfate). **Tablet (slow release):** 10 mg to 200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate).
Complementary list	
*methadone**	***Tablet:** 5 mg; 10 mg (hydrochloride).* ***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL (hydrochloride).* ***Concentrate for oral liquid:** 5 mg/mL; 10 mg/mL (hydrochloride)* * For the management of cancer pain.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
2.3 Medicines for other symptoms common in palliative care	
amitriptyline	**Tablet:** 10 mg; 25 mg.
cyclizine	**Injection:** 50 mg/mL. **Tablet:** 50 mg.
dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. **Oral liquid:** 2 mg/5 mL. **Tablet:** 2 mg.
diazepam	**Injection:** 5 mg/mL. **Oral liquid:** 2 mg/5 mL. **Rectal solution:** 2.5 mg; 5 mg; 10 mg. **Tablet:** 5 mg; 10 mg.
docusate sodium	**Capsule:** 100 mg. **Oral liquid:** 50 mg/5 mL.
fluoxetine [a]	**Solid oral dosage form:** 20 mg (as hydrochloride). [a] > 8 years.
hyoscine hydrobromide	**Injection:** 400 micrograms/mL; 600 micrograms/mL. Transdermal patches: 1 mg/72 hours.
lactulose	**Oral liquid:** 3.1 to 3.7 g/5 mL.
midazolam	**Injection:** 1 mg/mL; 5 mg/mL. **Oral liquid:** 2mg/mL. **Solid oral dosage form:** 7.5 mg; 15 mg.
☐ ondansetron [a] Therapeutic alternatives – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg base/mL in 2 mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] > 1 month.
senna	**Oral liquid:** 7.5 mg/5 mL.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.
☐ loratadine*	**Oral liquid:** 1 mg/mL.
Therapeutic alternatives: – cetirizine – fexofenadine	**Tablet:** 10 mg. * *There may be a role for sedating antihistamines for limited indications.*
☐ prednisolone	**Oral liquid:** 5 mg/mL.
Therapeutic alternatives: – prednisone	**Tablet:** 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Powder.**
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/mL in 10 mL ampoule. **Oral liquid:** 10%; 20%.
atropine	**Injection:** 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	**Injection:** 100 mg/mL in 10 mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1 mL ampoule.
Complementary List	
deferoxamine	***Powder for injection:** 500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:** 50 mg/mL in 2 mL ampoule.*
fomepizole	***Injection:** 5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.*
sodium calcium edetate	***Injection:** 200 mg/mL in 5 mL ampoule.*
succimer	***Solid oral dosage form:** 100 mg.*

5. ANTICONVULSANTS/ANTIEPILEPTICS

carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg.
diazepam	**Gel or rectal solution:** 5 mg/mL in 0.5 mL; 2 mL; 4 mL tubes.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. * For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
☐ lorazepam Therapeutic alternatives: – diazepam (injection) – midazolam (injection)	**Injection:** 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
midazolam	**Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL. **Ampoule*:** 1 mg/mL; 10 mg/mL. * For buccal administration when solution for oromucosal administration is not available
phenobarbital	**Injection:** 200 mg/mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/mL (sodium) in 5 mL vial. **Oral liquid:** 25 mg to 30 mg/5 mL.* **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium). **Tablet (chewable):** 50 mg. * The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
valproic acid (sodium valproate)* * *avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg.

5. ANTICONVULSANTS/ANTIEPILEPTICS *(continued)*

Complementary List

ethosuximide	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*
*valproic acid (sodium valproate)**	***Injection:*** *100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule.*

* *avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 *Intestinal anthelminthics*

albendazole	**Tablet (chewable):** 400 mg.
ivermectin	**Tablet (scored):** 3 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 600 mg.
pyrantel	**Oral liquid:** 50 mg (as embonate or pamoate)/mL. **Tablet (chewable):** 250 mg (as embonate or pamoate).

6.1.2 *Antifilarials*

albendazole	**Tablet (chewable):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet (scored):** 3 mg.

6.1.3 *Antischistosomals and other antitrematode medicines*

praziquantel	Tablet: 600 mg.
triclabendazole	Tablet: 250 mg.

Complementary List

*oxamniquine**	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*

* *For use when praziquantel treatment fails.*

6.1.4 *Cysticidal medicines*

Complementary List

albendazole	***Tablet (chewable):*** *400 mg.*
mebendazole	***Tablet (chewable):*** *500 mg.*
praziquantel	***Tablet:*** *500 mg; 600 mg*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics has been developed by WHO – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.1 ***Access group antibiotics***

<table>
<tr><td>amikacin</td><td colspan="2">Injection: 250 mg/mL (as sulfate) in 2 mL vial.</td></tr>
<tr><td></td><td>FIRST CHOICE
– High-risk febrile neutropenia
– Pyelonephritis (severe)</td><td>SECOND CHOICE
– Sepsis in neonates and children</td></tr>
<tr><td>amoxicillin</td><td colspan="2">Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.
Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate).
Solid oral dosage form: 250 mg; 500 mg (as trihydrate).</td></tr>
<tr><td></td><td>FIRST CHOICE
– Community acquired pneumonia (mild to moderate)
– Community acquired pneumonia (severe)
– Complicated severe acute malnutrition
– Otitis media
– Pharyngitis
– Progressive apical dental abscess
– Sepsis in neonates and children
– Sinusitis
– Uncomplicated severe acute malnutrition</td><td>SECOND CHOICE
– Acute bacterial meningitis</td></tr>
</table>

6. ANTI-INFECTIVE MEDICINES *(continued)*

amoxicillin + clavulanic acid

Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.

Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL.

Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Hospital acquired pneumonia* – *Low-risk febrile neutropenia* – *Lower urinary tract infections* – *Sinusitis* – *Skin and soft tissue infections*	– *Bone and joint infections* – *Community acquired pneumonia (mild to moderate)* – *Community acquired pneumonia (severe)* – *Otitis media* – *Surgical prophylaxis*

ampicillin

Powder for injection: 500 mg; 1 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections* – *Complicated severe acute malnutrition* – *Sepsis in neonates and children*	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

benzathine benzylpenicillin

Powder for injection: 1.2 million IU (≈ 900 mg) in vial; 2.4 million IU (≈ 1.8 g) in vial.

FIRST CHOICE	SECOND CHOICE
– *Syphilis (congenital)*	

benzylpenicillin

Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* – *Complicated severe acute malnutrition* – *Sepsis in neonates and children* – *Syphilis (congenital)*	– *Acute bacterial meningitis*

cefalexin

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (anhydrous).

Solid oral dosage form: 250 mg (as monohydrate).

FIRST CHOICE	SECOND CHOICE
– *Skin and soft tissue infections*	– *Pharyngitis*

cefazolin [a]

Powder for injection: 1 g (as sodium salt) in vial.

[a] > 1 month.

FIRST CHOICE	SECOND CHOICE
– *Surgical prophylaxis*	– *Bone and joint infections*

chloramphenicol

Capsule: 250 mg.

Oily suspension for injection*: 0.5 g/mL (as sodium succinate) in 2 mL ampoule.

* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.

Oral liquid: 150 mg/5 mL (as palmitate).

Powder for injection: 1 g (sodium succinate) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

clindamycin

Capsule: 150 mg (as hydrochloride).
Injection: 150 mg/mL (as phosphate).
Oral liquid: 75 mg/5 mL (as palmitate).

FIRST CHOICE	SECOND CHOICE
– *Necrotizing fasciitis*	– *Bone and joint infections*

☐ cloxacillin*

Therapeutic alternatives:
– 4th level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)

Capsule: 500 mg; 1 g (as sodium).
Powder for injection: 500 mg (as sodium) in vial.
Powder for oral liquid: 125 mg/5 mL (as sodium).
* cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
– *Bone and joint infections* – *Skin and soft tissue infections*	– *Sepsis in neonates and children*

doxycycline [a]

Oral liquid: 25 mg/5 mL; 50 mg/5 mL (anhydrous).
Powder for injection: 100 mg in vial.
Solid oral dosage form: 50 mg; 100 mg (as hyclate).
[a] Use in children <8 years only for life-threatening infections when no alternative exists.

FIRST CHOICE	SECOND CHOICE
	– *Cholera* – *Community acquired pneumonia (mild to moderate)*

gentamicin

Injection: 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis in neonates* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections* – *Complicated severe acute malnutrition* – *Sepsis in neonates and children*	– *Surgical prophylaxis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

metronidazole	**Injection:** 500 mg in 100 mL vial. **Oral liquid:** 200 mg/5 mL (as benzoate). **Tablet:** 200 mg to 500 mg.	
	FIRST CHOICE – *C. difficile infection* – *Complicated intra-abdominal infections (mild to moderate)* – *Complicated intra-abdominal infections (severe)* – *Necrotizing fasciitis* – *Surgical prophylaxis*	**SECOND CHOICE** – *Complicated intra-abdominal infections (mild to moderate)*
nitrofurantoin	**Oral liquid:** 25 mg/5 mL. **Tablet:** 100 mg.	
	FIRST CHOICE – *Lower urinary tract infections*	**SECOND CHOICE**
phenoxymethylpenicillin	**Powder for oral liquid:** 250 mg/5 mL (as potassium). **Tablet:** 250 mg (as potassium).	
	FIRST CHOICE – *Community acquired pneumonia (mild to moderate)* – *Pharyngitis* – *Progressive apical dental abscess*	**SECOND CHOICE**
procaine benzylpenicillin*	**Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial. * Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis / sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.	
	FIRST CHOICE – *Syphilis (congenital)*	**SECOND CHOICE**

6. ANTI-INFECTIVE MEDICINES *(continued)*		
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/ mL in 5 mL ampoule; 80 mg + 16 mg/ mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg.	
	FIRST CHOICE – *Lower urinary tract infections*	**SECOND CHOICE** – *Acute invasive bacterial diarrhoea / dysentery*
trimethoprim	**Tablet:** 100 mg; 200 mg. **Oral liquid:** 50 mg/5 mL.	
	FIRST CHOICE – *Lower urinary tract infections*	**SECOND CHOICE**
6.2.2 ***Watch group antibiotics***		
azithromycin	**Capsule:** 250 mg; 500 mg (anhydrous). **Oral liquid:** 200 mg/5 mL.	
	FIRST CHOICE – *Cholera* – *Enteric fever* – *Trachoma* – *Yaws*	**SECOND CHOICE** – *Acute invasive bacterial diarrhoea / dysentery*
cefixime	**Powder for oral liquid:** 100 mg/5 mL. **Solid oral dosage form:** 200 mg; 400 mg (as trihydrate).	
	FIRST CHOICE	**SECOND CHOICE** – *Acute invasive bacterial diarrhoea / dysentery*

6. ANTI-INFECTIVE MEDICINES *(continued)*

cefotaxime*

Powder for injection: 250 mg (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intraabdominal infections (severe)* – *Hospital acquired pneumonia* – *Pyelonephritis (severe)*	– *Bone and joint infections* – *Pyelonephritis (mild to moderate)* – *Sepsis in neonates and children*

ceftriaxone* [a]

Powder for injection: 250 mg; 1 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intraabdominal infections (severe)* – *Endophthalmitis* – *Enteric fever* – *Hospital acquired pneumonia* – *Necrotizing fasciitis* – *Pyelonephritis (severe)*	– *Acute invasive bacterial diarrhoea / dysentery* – *Bone and joint infections* – *Pyelohepnritis or prostatitis (mild to moderate)* – *Sepsis in neonates and children*

6. ANTI-INFECTIVE MEDICINES *(continued)*		
cefuroxime	**Powder for injection:** 250 mg; 750 mg; 1.5 g (as sodium) in vial.	
	FIRST CHOICE	**SECOND CHOICE** Surgical prophylaxis
ciprofloxacin	**Oral liquid:** 250 mg/5 mL (anhydrous). **Solution for IV infusion:** 2 mg/mL (as hyclate). **Solid oral dosage form:** 250 mg (as hydrochloride).	
	FIRST CHOICE – *Acute invasive bacterial diarrhoea / dysentery* – *Enteric fever* – *Low-risk febrile neutropenia* – *Pyelonephritis (mild to moderate)*	**SECOND CHOICE** – *Cholera* – *Complicated intraabdominal infections (mild to moderate)*
☐ clarithromycin Therapeutic alternatives: – erythromycin	**Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL. **Powder for injection:** 500 mg in vial. **Solid oral dosage form:** 500 mg.	
	FIRST CHOICE	**SECOND CHOICE** – *Pharyngitis*
piperacillin + tazobactam	**Powder for injection:** 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.	
	FIRST CHOICE – *Complicated intraabdominal infections (severe)* – *High-risk febrile neutropenia* – *Hospital acquired pneumonia* – *Necrotizing fasciitis*	**SECOND CHOICE**
vancomycin	Capsule: 125 mg; 250 mg (as hydrochloride).	
	FIRST CHOICE	**SECOND CHOICE** – *C. difficile infection*

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

ceftazidime

Powder for injection: *250 mg; 1 g (as pentahydrate) in vial.*

FIRST CHOICE	SECOND CHOICE
– *Endophthalmitis*	

☐ *meropenem** [a]

Powder for injection: *500 mg (as trihydrate); 1 g (as trihydrate) in vial*

[a] > 3 months.

Therapeutic alternatives:*

– *imipenem + cilastatin*

* *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.*

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis in neonates* – *Complicated intraabdominal infections (severe)* – *High-risk febrile neutropenia*

vancomycin

Powder for injection: *250 mg (as hydrochloride) in vial.*

FIRST CHOICE	SECOND CHOICE
– *Endophthalmitis* – *Necrotizing fasciitis*	– *High-risk febrile neutropenia*

6.2.3 *Reserve group antibiotics*

Complementary List

ceftazidime + avibactam — ***Powder for injection:*** *2 g + 0.5 g in vial.*

colistin — ***Powder for injection:*** *1 million IU (as colistemethate sodium) in vial.*

fosfomycin — ***Powder for injection:*** *2 g; 4 g (as sodium) in vial.*

linezolid — ***Injection for intravenous administration:*** *2 mg/mL in 300 mL bag.*
Powder for oral liquid: *100 mg/5 mL.*
Tablet: *400 mg; 600 mg.*

polymyxin B — ***Powder for injection:*** *500,000 IU in vial.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.4 ***Antileprosy medicines***

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Capsule:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Solid oral dosage form:** 150 mg; 300 mg.

6.2.5 ***Antituberculosis medicines***

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	**Oral liquid:** 25 mg/mL. **Tablet:** 100 mg; 400 mg (hydrochloride). **Tablet (dispersible):** 100 mg.
isoniazid	**Oral liquid:** 50 mg/5 mL. **Tablet:** 100 mg; 300 mg. **Tablet (dispersible):** 100 mg.
isoniazid + pyrazinamide + rifampicin	**Tablet (dispersible):** 50 mg + 150 mg + 75 mg.
isoniazid + rifampicin	**Tablet (dispersible):** 50 mg + 75 mg.
isoniazid + rifapentine	**Tablet (scored):** 300 mg + 300 mg.
pyrazinamide	**Oral liquid:** 30 mg/mL. **Tablet:** 400 mg; 500 mg. **Tablet (dispersible):** 150 mg.
rifampicin	**Oral liquid:** 20 mg/mL. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine	**Tablet:** 150 mg; 300 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin	***Injection:*** *100 mg/2 mL (as sulfate) in 2 mL vial; 250 mg/mL (as sulfate) in 2 mL vial.*
*amoxicillin + clavulanic acid**	***Powder for oral liquid:*** *250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5 mL.* ***Tablet:*** *500 mg (as trihydrate) + 125 mg (as potassium salt).* * *For use only in combination with meropenem.*
bedaquiline [a]	***Tablet:*** *20 mg;100 mg.* [a] ≥ 5 years
clofazimine	***Solid oral dosage form:*** *50 mg; 100 mg.*
cycloserine	***Solid oral dosage form:*** *125 mg; 250 mg.*
delamanid [a]	***Tablet (dispersible):*** *25 mg.* [a] ≥3 years ***Tablet:*** *50 mg.* [a] ≥6 years
☐ *ethionamide* *Therapeutic alternatives:* *– protionamide*	***Tablet:*** *125 mg; 250 mg.* ***Tablet (dispersible):*** *125 mg.*
levofloxacin	***Tablet:*** *250 mg; 500 mg.* ***Tablet (dispersible):*** *100 mg.*
linezolid	***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *600 mg.* ***Tablet (dispersible):*** *150 mg.*
meropenem	***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*
moxifloxacin	***Tablet:*** *400 mg.* ***Tablet (dispersible):*** *100 mg.*
p-aminosalicylic acid	***Granules:*** *4 g in sachet.*
streptomycin	***Powder for injection:*** *1 g (as sulfate) in vial.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.3 Antifungal medicines

amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
fluconazole	**Capsule:** 50 mg. **Injection:** 2 mg/mL in vial. **Oral liquid:** 50 mg/5 mL.
flucytosine	**Capsule:** 250 mg. **Infusion:** 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL. **Solid oral dosage form:** 125 mg; 250 mg.
itraconazole*	**Capsule:** 100 mg. **Oral liquid:** 10 mg/mL. * For treatment of chronic pulmonary aspergillosis, acute invasive aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 50 mg/5 mL; 100 000 IU/mL. **Tablet:** 100 000 IU; 500 000 IU.
voriconazole*	**Tablet:** 50 mg; 200 mg. **Powder for injection:** 200 mg in vial. **Powder for oral liquid:** 40 mg/mL. * For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.

Complementary List

☐ *micafungin* *Therapeutic alternatives:* – *anidulafungin* – *caspofungin*	***Powder for injection:*** *50 mg (as sodium); 100 mg (as sodium) in vial.*
potassium iodide	***Saturated solution.***

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4 Antiviral medicines

6.4.1 *Antiherpes medicines*

aciclovir	**Oral liquid:** 200 mg/5 mL. **Powder for injection:** 250 mg (as sodium salt) in vial. **Tablet:** 200 mg.

6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

lamivudine	**Oral liquid:** 50 mg/5 mL.
zidovudine	**Oral liquid:** 50 mg/5 mL.

6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

nevirapine [a]	**Oral liquid:** 50 mg/5 mL. **Tablet (dispersible):** 50 mg. [a] > 6 weeks

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.3 ***Protease inhibitors***

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

darunavir [a]	**Tablet:** 75 mg. [a] > 3 years
lopinavir + ritonavir	**Solid oral dosage form:** 40 mg + 10 mg. **Tablet (heat stable):** 100 mg + 25 mg.
ritonavir	**Tablet (heat stable):** 25 mg; 100 mg.

6.4.2.4 ***Integrase inhibitors***

dolutegravir [a]	**Tablet (dispersible, scored):** 10 mg. [a] ≥4 weeks and ≥3 kg **Tablet:** 50 mg. [a] ≥ 25 kg
raltegravir*	**Granules for oral suspension:** 100 mg in sachet. **Tablet (chewable):** 25 mg. * For use in second-line regimens in accordance with WHO treatment guidelines.

6.4.2.5 ***Fixed-dose combinations of antiretroviral medicines***

abacavir + lamivudine	**Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg.
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg.

6.4.2.6 ***Medicines for prevention of HIV-related opportunistic infections***

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.3 *Other antivirals*

ribavirin	**Injection for intravenous administration:** 800 mg and 1 g in 10 mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of viral haemorrhagic fevers only.

Complementary List

*oseltamivir**	***Capsule:** 30 mg; 45 mg; 75 mg (as phosphate).* * *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.*
*valganciclovir**	***Powder for oral solution:** 50 mg/mL* ***Tablet:** 450 mg.* * *For the treatment of cytomegalovirus retinitis (CMVr).*

6.4.4 *Antihepatitis medicines*

6.4.4.1 *Medicines for hepatitis B*

6.4.4.1.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

entecavir	**Oral liquid:** 0.05 mg/mL. **Tablet:** 0.5 mg; 1 mg.

6.4.4.2 *Medicines for hepatitis C*

Pangenotypic direct-acting antivirals should be considered as therapeutically equivalent for the purposes of selection and procurement at national level.

6.4.4.2.1 ☐ *Pangenotypic direct-acting antiviral combinations*

daclatasvir*	**Tablet:** 30 mg; 60 mg (as hydrochloride). * Pangenotypic when used in combination with sofosbuvir.
daclatasvir + sofosbuvir	**Tablet:** 60 mg + 400 mg.
glecaprevir + pibrentasvir	**Granules:** 50 mg + 20 mg in sachet. **Tablet:** 100 mg + 40 mg.
sofosbuvir*	**Tablet:** 200 mg; 400 mg. * Pangenotypic when used in combination with daclatasvir.
sofosbuvir + velpatasvir	**Tablet:** 200 mg + 50 mg; 400 mg + 100 mg.

~~***6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations***~~

~~***6.4.4.2.3 Other antivirals for hepatitis C***~~

6. ANTI-INFECTIVE MEDICINES *(continued)*	
6.5 Antiprotozoal medicines	
6.5.1 ***Antiamoebic and antigiardiasis medicines***	
diloxanide [a]	**Tablet:** 500 mg (furoate). [a] > 25 kg.
☐ metronidazole Therapeutic alternatives: – tinidazole	**Injection:** 500 mg in 100 mL vial. **Oral liquid:** 200 mg/5 mL (as benzoate). **Tablet:** 200 mg to 500 mg.
6.5.2 ***Antileishmaniasis medicines***	
amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as sulfate).
sodium stibogluconate **or** meglumine antimoniate	**Injection:** 100 mg/mL, 1 vial = 30 mL **or** 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5 mL ampoule.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.3 *Antimalarial medicines*

6.5.3.1 *For curative treatment*

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
artemether*	**Oily injection:** 80 mg/mL in 1 mL ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Rectal dosage form:** 50 mg; 100 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care). **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
artesunate + amodiaquine*	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. * Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
artesunate + pyronaridine tetraphosphate [a]	**Granules:** 20 mg + 60 mg. **Tablet:** 60 mg + 180 mg. [a] > 5 kg
chloroquine*	**Oral liquid:** 50 mg/5 mL (as phosphate or sulfate). **Tablet:** 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of *Plasmodium vivax* infection.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
dihydroartemisinin + piperaquine phosphate [a]	**Tablet:** 20 mg + 160 mg; 40 mg + 320 mg. [a] > 5 kg
doxycycline*	**Capsule:** 100 mg (as hydrochloride or hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *Plasmodium vivax* and *Plasmodium ovale infections*, given for 14 days.
quinine*	**Injection:** 300 mg/mL (hydrochloride) in 2 mL ampoule. **Tablet:** 300 mg (sulfate) or 300 mg (bisulfate). * For use only in the management of severe malaria and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	**Tablet:** 500 mg + 25 mg. *Only in combination with artesunate 50 mg.
6.5.3.2 ***For chemoprevention***	
amodiaquine – sulfadoxine + pyrimethamine	**Co-packaged dispersible tablets:** amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	**Oral liquid:** 50 mg/5 mL (as phosphate or sulfate). **Tablet:** 150 mg (as phosphate or sulfate). * For use only for the treatment of *Plasmodium vivax* infection.
doxycycline [a]	**Solid oral dosage form:** 100 mg (as hydrochloride or hyclate). [a] > 8 years.
mefloquine [a]	**Tablet:** 250 mg (as hydrochloride). [a] > 5 kg or > 3 months.
proguanil*	**Tablet:** 100 mg (as hydrochloride). * For use only in combination with chloroquine.
sulfadoxine + pyrimethamine	**Tablet:** 250 mg + 12.5 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.4 *Antipneumocystosis and antitoxoplasmosis medicines*

pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg.

6.5.5 *Antitrypanosomal medicines*

6.5.5.1 *African trypanosomiasis*

fexinidazole*	**Tablet:** 600 mg * For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

Medicines for the treatment of 1st stage African trypanosomiasis.

pentamidine*	**Powder for injection:** 200 mg (as isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	**Powder for injection:** 1 g in vial. * To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg/mL (hydrochloride) in 100 mL bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
nifurtimox*	**Tablet:** 120 mg. * Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.
Complementary List	
melarsoprol	***Injection:*** *180 mg/5 mL in 5 mL ampoule (3.6% solution).*

6. ANTI-INFECTIVE MEDICINES *(continued)*	
6.5.5.2 ***American trypanosomiasis***	
benznidazole	**Tablet:** 12.5 mg; 100 mg. **Tablet (scored):** 50 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg; 250 mg.
6.6 Medicines for ectoparasitic infections	
ivermectin	**Tablet (scored):** 3 mg
7. ANTIMIGRAINE MEDICINES	
7.1 For treatment of acute attack	
ibuprofen	**Tablet:** 200 mg; 400 mg.
paracetamol	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Tablet:** 300 mg to 500 mg.
7.2 For prophylaxis	
propranolol	**Tablet:** 20 mg; 40 mg (hydrochloride).
8. IMMUNOMODULATORS AND ANTINEOPLASTICS	
8.1 Immunomodulators for non-malignant disease	
Complementary List	
☐ *adalimumab**	***Injection:*** *40 mg/0.8 mL; 40 mg/0.4 mL.*
Therapeutic alternatives:* – *etanercept* – *infliximab* * *including quality-assured biosimilars*	
azathioprine	***Powder for injection:*** *100 mg (as sodium salt) in vial.* ***Tablet (scored):*** *50 mg.*
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/mL in 1 mL ampoule.*
tacrolimus	***Capsule (immediate-release):*** *0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg.* ***Granules for oral supsension:*** *0.2 mg; 1 mg.* ***Injection:*** *5 mg/mL in 1 mL vial.*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2 Antineoplastic and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

8.2.1 *Cytotoxic medicines*

Complementary List

arsenic trioxide	***Concentrate for solution for infusion:*** *1 mg/mL* – *Acute promyelocytic leukaemia*
*asparaginase**	***Powder for injection:*** *10 000 IU in vial.* – *Acute lymphoblastic leukaemia*
* *including quality-assured biosimilars*	
bleomycin	***Powder for injection:*** *15 mg (as sulfate) in vial.* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Ovarian germ cell tumours* – *Testicular germ cell tumours*
calcium folinate	***Injection:*** *3 mg/mL in 10 mL ampoule.* ***Tablet:*** *5 mg; 15 mg; 25 mg.* – *Burkitt lymphoma* – *Osteosarcoma*
carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Retinoblastoma* – *Testicular germ cell tumours*
cisplatin	***Injection:*** *10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100mL.* – *Low-grade glioma* – *Nasopharyngeal cancer* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Testicular germ cell tumours*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
cyclophosphamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* ***Tablet:*** *25 mg; 50 mg.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
cytarabine	***Powder for injection:*** *100 mg in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Acute promyelocytic leukaemia* – *Burkitt lymphoma*
dacarbazine	***Powder for injection:*** *100 mg in vial.* – *Hodgkin lymphoma*
dactinomycin	***Powder for injection:*** *500 micrograms in vial.* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
daunorubicin	***Powder for injection:*** *50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia.*
doxorubicin	***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
etoposide	***Capsule:*** *50 mg; 100 mg.* ***Injection:*** *20 mg/mL in 5 mL ampoule.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Burkitt lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Retinoblastoma* – *Testicular germ cell tumours*
fluorouracil	***Injection:*** *50 mg/mL in 5 mL ampoule.* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic colorectal cancer* – *Nasopharyngeal cancer*
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.* – *Chronic myeloid leukaemia*
ifosfamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Rhabdomyosarcoma* – *Testicular germ cell tumours*
irinotecan	***Injection:*** *40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.* – *Metastatic colorectal cancer* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
mercaptopurine	***Tablet:*** *50 mg.* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
methotrexate	***Powder for injection:*** *50 mg (as sodium salt) in vial.* ***Tablet:*** *2.5 mg (as sodium salt).* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia* – *Burkitt lymphoma* – *Osteosarcoma*
oxaliplatin	***Injection:*** *50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.* ***Powder for injection:*** *50 mg; 100 mg in vial.* – *Early stage colon cancer* – *Metastatic colorectal cancer*
paclitaxel	***Injection:*** *6 mg/mL in vial.* – *Ovarian germ cell tumours*
*pegaspargase**	***Injection:*** *3,750 units/5 mL in vial.* – *Acute lymphoblastic leukaemia.*
* *including quality-assured biosimilars*	
procarbazine	***Capsule:*** *50 mg (as hydrochloride).* – *Hodgkin lymphoma*
realgar-Indigo naturalis formulation	***Tablet:*** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).* – *Acute promyelocytic leukaemia*
tioguanine	***Solid oral dosage form:*** *40 mg.* – *Acute lymphoblastic leukaemia*
vinblastine	***Injection:*** *10 mg/10 mL (sulfate) in vial.* ***Powder for injection:*** *10 mg (sulfate) in vial.* – *Hodgkin lymphoma* – *Low-grade glioma* – *Ovarian germ cell tumours* – *Testicular germ cell tumours*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
vincristine	***Injection:*** *1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.* ***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Retinoblastoma* – *Rhabdomyosarcoma*
vinorelbine	***Capsule:*** *20 mg; 30 mg; 80 mg.* ***Injection:*** *10 mg/mL in 1 mL vial; 50 mg/5 mL in 5 mL vial.* – *Rhabdomyosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.2 *Targeted therapies*

Complementary List

all-trans retinoid acid (ATRA)	***Capsule:*** *10 mg.* – *Acute promyelocytic leukaemia*
dasatinib	***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
everolimus	***Tablet:*** *2.5 mg; 5 mg; 7.5 mg; 10 mg.* ***Tablet (dispersible):*** *2 mg; 3 mg; 5 mg.* – *Subependymal giant cell astrocytoma*
imatinib	***Solid oral dosage form:*** *100 mg; 400 mg.* – *Chronic myeloid leukaemia* – *Gastrointestinal stromal tumour* – *Philadelphia chromosome positive acute lymphoblastic leukaemia*
nilotinib	***Capsule:*** *150 mg; 200 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
*rituximab** * *including quality-assured biosimilars*	***Injection (intravenous):*** *100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.* – *Diffuse large B-cell lymphoma*

8.2.3 *Immunomodulators*

Complementary List

*filgrastim** * *including quality-assured biosimilars*	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.* ***Injection:*** *300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.4 *Hormones and antihormones*

Complementary List

dexamethasone	***Injection:*** *4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.* ***Oral liquid:*** *2 mg/5 mL.* ***Tablet:*** *2 mg; 4 mg.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma*
hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma*
methylprednisolone	***Injection:*** *40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.* – *Acute lymphoblastic leukamia* – *Burkitt lymphoma*
☐ *prednisolone* *Therapeutic alternatives:* – *prednisone*	***Oral liquid:*** *5 mg/mL.* ***Tablet:*** *5 mg; 25 mg.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Hodgkin lymphoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.5 *Supportive medicines*

Complementary List

allopurinol	***Tablet:*** *100 mg; 300 mg.* – *Tumour lysis syndrome*
mesna	***Injection:*** *100 mg/mL in 4 mL and 10 mL ampoules.* ***Tablet:*** *400 mg; 600 mg.* – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Rhabdomyosarcoma* – *Testicular germ cell tumours*
rasburicase	***Powder and solvent for solution for infusion:*** *1.5 mg; 7.5 mg in vial.* – *Tumour lysis syndrome*

~~9. ANTIPARKINSONISM MEDICINES~~

10. MEDICINES AFFECTING THE BLOOD

10.1 Antianaemia medicines

ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/mL. **Tablet:** equivalent to 60 mg iron.
folic acid	**Tablet:** 1 mg; 5 mg.
hydroxocobalamin	**Injection:** 1 mg (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.

Complementary List

☐ *erythropoiesis-stimulating agents** *Therapeutic alternatives:* – *epoetin alfa, beta and theta* – *darbepoetin alfa* * *including quality-assured biosimilars*	***Injection:*** *pre-filled syringe* *1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.*

10. MEDICINES AFFECTING THE BLOOD *(continued)*

10.2 Medicines affecting coagulation

☐ enoxaparin Therapeutic alternatives: – dalteparin – nadroparin * *including quality-assured biosimilars*	**Injection:** ampoule or pre-filled syringe 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.
phytomenadione	**Injection:** 1 mg/mL; 10 mg/mL in ampoule. **Tablet:** 10 mg.
Complementary List	
desmopressin	***Injection:*** *4 micrograms/mL (as acetate) in 1 mL ampoule.* ***Nasal spray:*** *10 micrograms (as acetate) per dose.*
heparin sodium	***Injection:*** *1000 IU/mL; 5000 IU/mL in 1 mL ampoule.*
protamine sulfate	***Injection:*** *10 mg/mL in 5 mL ampoule.*
☐ *warfarin* *Therapeutic alternatives to be reviewed (2023)*	***Tablet:*** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium).*

10.3 Other medicines for haemoglobinopathies

Complementary list	
☐ *deferoxamine**	***Powder for injection:*** *500 mg (mesilate) in vial.*
Therapeutic alternatives: *– deferasirox (oral)*	
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 500 mg; 1 g.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh-frozen plasma	
platelets	
red blood cells	
whole blood	

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11.2.1 *Human immunoglobulins*

anti-rabies immunoglobulin	**Injection:** 150 IU/mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	
normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.** ***Intravenous administration:*** *5%; 10% protein solution.*** ***Subcutaneous administration:*** *15%; 16% protein solution.** * *Indicated for primary immune deficiency.* ** *Indicated for primary immune deficiency and Kawasaki disease.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES *(continued)*

11.2.2 *Blood coagulation factors*

Complementary List

☐ *coagulation factor VIII* *Therapeutic alternatives to be reviewed (2023)*	***Powder for injection:*** *500 IU/vial.*
☐ *coagulation factor IX* *Therapeutic alternatives to be reviewed (2023)*	***Powder for injection:*** *500 IU/vial; 1000 IU/vial.*

11.3 Plasma substitutes

☐ dextran 70 Therapeutic alternatives: – Polygeline injectable solution 3.5%	**Injectable solution:** 6%.

12. CARDIOVASCULAR MEDICINES

~~**12.1 Antianginal medicines**~~

~~**12.2 Antiarrhythmic medicines**~~

12.3 Antihypertensive medicines

☐ enalapril Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).

12.4 Medicines used in heart failure

digoxin	**Injection:** 250 micrograms/mL in 2 mL ampoule. **Oral liquid:** 50 micrograms/mL. **Tablet:** 62.5 micrograms; 250 micrograms.
furosemide	**Injection:** 10 mg/mL in 2 mL ampoule. **Oral liquid:** 20 mg/5 mL. **Tablet:** 40 mg.

Complementary List

dopamine	***Injection:*** *40 mg/mL (hydrochloride) in 5 mL vial.*

~~**12.5 Antithrombotic medicines**~~

~~**12.6 Lipid-lowering agents**~~

13. DERMATOLOGICAL MEDICINES (topical)

13.1 Antifungal medicines

☐ miconazole Therapeutic alternatives: – 4th level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	**Cream or ointment:** 2% (nitrate).
terbinafine	**Cream or ointment:** 1% (hydrochloride).

13.2 Anti-infective medicines

mupirocin	**Cream:** 2% (as calcium). **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] > 2 months.

13.3 Anti-inflammatory and antipruritic medicines

☐ betamethasone [a] Therapeutic alternatives: – 4th level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
calamine	**Lotion.**
hydrocortisone	**Cream or ointment:** 1% (acetate).

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*	
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	**Cream or lotion:** 5%.
☐ calcipotriol Therapeutic alternatives: – calcitriol – tacalcitol	**Cream or ointment:** 50 micrograms/mL (0.005%). **Lotion:** 50 micrograms/mL (0.005%).
coal tar	**Solution:** 5%.
☐ podophyllum resin Therapeutic alternatives: – - podophyllotoxin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.
urea	**Cream or ointment:** 5%; 10%.
13.5 Scabicides and pediculicides	
☐ benzyl benzoate [a] Therapeutic alternatives: – precipitated sulfur topical ointment	**Lotion:** 25%. [a] > 2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.
14. DIAGNOSTIC AGENTS	
14.1 Ophthalmic medicines	
fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide Therapeutic alternatives: – atropine – cyclopentolate	**Eye drops:** 0.5%.
14.2 Radiocontrast media	
Complementary List	
barium sulfate	***Aqueous suspension.***

15. ANTISEPTICS AND DISINFECTANTS

15.1 Antiseptics

☐ chlorhexidine Therapeutic alternatives to be reviewed (2023)	**Solution:** 5% (digluconate).
☐ ethanol Therapeutic alternatives: – propanol	**Solution:** 70% (denatured).
☐ povidone iodine Therapeutic alternatives: – iodine	**Solution:** 10% (equivalent to 1% available iodine).

15.2 Disinfectants

alcohol based hand rub	**Solution** containing ethanol 80% volume /volume. **Solution** containing isopropyl alcohol 75% volume/ volume.
chlorine base compound	**Liquid:** (0.1% available chlorine) for solution. **Powder:** (0.1% available chlorine) for solution. **Solid:** (0.1% available chlorine) for solution.
☐ chloroxylenol Therapeutic alternatives: – 4th level ATC chemical subgroup (D08AE Phenol and derivatives)	**Solution:** 4.8%.
glutaral	**Solution:** 2%.

16. DIURETICS	
furosemide	**Injection:** 10 mg/mL in 2 mL ampoule. **Oral liquid:** 20 mg/5 mL. **Tablet:** 10 mg; 20 mg; 40 mg.
Complementary List	
☐ *hydrochlorothiazide* *Therapeutic alternatives:* – *chlorothiazide* – *chlortalidone*	***Tablet (scored):** 25 mg.*
mannitol	***Injectable solution:** 10%; 20%.*
spironolactone	***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.* ***Tablet:** 25 mg.*

17. GASTROINTESTINAL MEDICINES

Complementary List

pancreatic enzymes	*Age-appropriate formulations and doses including lipase, protease and amylase.*

17.1 Antiulcer medicines

☐ omeprazole Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	Powder for oral liquid: 20 mg; 40 mg sachets. Solid oral dosage form: 10 mg; 20 mg; 40 mg.
☐ ranitidine Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BA H2-receptor antagonists) excluding combinations	**Injection:** 25 mg/mL (as hydrochloride) in 2 mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/mL in 1 mL ampoule (as disodium phosphate salt). **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL. **Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide [a]	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL. **Tablet:** 10 mg (hydrochloride). [a] Not in neonates.
☐ ondansetron [a] Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg base/mL in 2 mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] > 1 month.

Complementary list

aprepitant	***Capsule:*** *80 mg; 125 mg; 165 mg.* ***Powder for oral suspension:*** *125 mg in sachet.*

17. GASTROINTESTINAL MEDICINES *(continued)*

~~**17.3 Anti-inflammatory medicines**~~

~~**17.4 Laxatives**~~

17.5 Medicines used in diarrhoea

oral rehydration salts – zinc sulfate	**Co-package containing:** **ORS powder for dilution** (see Section 17.5.1) – zinc sulfate **solid oral dosage form** 20 mg (see Section 17.5.2)

17.5.1 *Oral rehydration*

oral rehydration salts	**Powder for dilution** in 200 mL; 500 mL; 1 L.

glucose:	75 mEq
sodium:	75 mEq or mmol/L
chloride:	65 mEq or mmol/L
potassium:	20 mEq or mmol/L
citrate:	10 mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

* trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

17.5.2 *Medicines for diarrhoea*

zinc sulfate*	**Solid oral dosage form:** 20 mg.

* In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts.

18. MEDICINES FOR ENDOCRINE DISORDERS

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	**Tablet:** 100 micrograms (acetate).
hydrocortisone	**Tablet:** 5 mg; 10 mg; 20 mg.

~~18.2 Androgens~~

~~18.3 Estrogens~~

~~18.4 Progestogens~~

18.5 Medicines for diabetes

18.5.1 *Insulins*

insulin injection (soluble)* * *including quality-assured biosimilars*	**Injection:** 100 IU/mL in 10 mL vial.
intermediate-acting insulin* * *including quality-assured biosimilars*	**Injection:** 100 IU/mL in 10 mL vial (as compound insulin zinc suspension or isophane insulin).
☐ long-acting insulin analogues* Therapeutic alternatives: – insulin detemir – insulin degludec – insulin glargine * *including quality-assured biosimilars*	**Injection:** 100 IU/mL in 3 mL cartridge or pre-filled pen.

18.5.2 *Oral hypoglycaemic agents*

Complementary List

metformin	***Tablet:** 500 mg (hydrochloride).*

18.6 Medicines for hypoglycaemia

glucagon	**Injection:** 1 mg/mL.

Complementary List

diazoxide	***Oral liquid:** 50 mg/mL* ***Tablet:** 50 mg*

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

18.7 Thyroid hormones and antithyroid medicines

levothyroxine	**Tablet:** 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).
Complementary List	
Lugol's solution	***Oral liquid:*** *about 130 mg total iodine/mL.*
☐ *methimazole* *Therapeutic alternatives:* – *carbimazole (depending on local availability)*	***Tablet:*** *5 mg; 10 mg; 20 mg.*
potassium iodide	***Tablet:*** *60 mg.*
*propylthiouracil**	***Tablet:*** *50 mg.* * *For use when alternative first-line treatment is not appropriate or available*

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	**Injection**.

19.2 Sera, immunoglobulins and monoclonal antibodies

All plasma fractions should comply with the WHO requirements.

anti-rabies virus monoclonal antibodies* * *including quality-assured biosimilars*	**Injection:** 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human). **Injection:** 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
antivenom immunoglobulin*	**Injection.** *Exact type to be defined locally.
diphtheria antitoxin	**Injection:** 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	**Injection:** 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial

19. IMMUNOLOGICALS *(continued)*

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at September 2020. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.
WHO noted the need for vaccines used in children to be polyvalent.

Recommendations for all

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

human papilloma virus (HPV) vaccine

measles vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

19. IMMUNOLOGICALS *(continued)*	
Recommendations for certain regions	
Japanese encephalitis vaccine	
tick-borne encephalitis vaccine	
yellow fever vaccine	
Recommendations for some high-risk populations	
cholera vaccine	
dengue vaccine	
hepatitis A vaccine	
meningococcal meningitis vaccine	
rabies vaccine	
typhoid vaccine	
Recommendations for immunization programmes with certain characteristics	
influenza vaccine (seasonal)	
mumps vaccine	
varicella vaccine	
20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
neostigmine	**Injection:** 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg/mL (chloride) in 2 mL ampoule. **Powder for injection:** (chloride), in vial.
☐ vecuronium Therapeutic alternatives to be reviewed (2023)	**Powder for injection:** 10 mg (bromide) in vial.
Complementary List	
pyridostigmine	***Injection:** 1 mg in 1 mL ampoule.* ***Tablet:** 60 mg (bromide).*

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% w/w.
azithromycin	**Solution (eye drops):** 1.5%. – *Trachoma*
erythromycin	**Ointment:** 0.5%. – *Infections due to Chlamydia trachomatis or Neisseria gonorrhoeae*
☐ gentamicin Therapeutic alternatives: – amikacin – kanamycin – netilmicin – tobramycin	**Solution (eye drops):** 0.3% (sulfate). – *Bacterial blepharitis* – *Bacterial conjunctivitis*
natamycin	**Suspension (eye drops):** 5%. – *Fungal keratitis*
☐ ofloxacin Therapeutic alternatives: – 4th level ATC chemical subgroup (S01AE Fluoroquinolones)	**Solution (eye drops):** 0.3%. – *Bacterial conjunctivitis* – *Bacterial keratitis*
☐ tetracycline Therapeutic alternatives: – chlortetracycline – oxytetracycline	**Eye ointment:** 1% (hydrochloride). – *Bacterial blepharitis* – *Bacterial conjunctivitis* – *Bacterial keratitis* – *Trachoma*

21.2 Anti-inflammatory agents

☐ prednisolone Therapeutic alternatives to be reviewed (2023)	**Solution (eye drops):** 0.5% (sodium phosphate).

21.3 Local anaesthetics

☐ tetracaine [a] Therapeutic alternatives: – 4th level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	**Solution (eye drops):** 0.5% (hydrochloride). [a] Not in preterm neonates.

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*	
~~**21.4 Miotics and antiglaucoma medicines**~~	
21.5 Mydriatics	
☐ atropine [a] Therapeutic alternatives: – homatropine hydrobromide – cyclopentolate hydrochloride	**Solution** (eye drops): 0.1%; 0.5%; 1% (sulfate). [a] > 3 months.
Complementary List	
epinephrine (adrenaline)	***Solution (eye drops):** 2% (as hydrochloride).*
~~**21.6 Anti-vascular endothelial growth factor (VEGF) preparations**~~	
22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE	
~~**22.1 Contraceptives**~~	
~~**22.2 Ovulation inducers**~~	
~~**22.3 Uterotonics**~~	
~~**22.4 Antioxytocics (tocolytics)**~~	
~~**22.5 Other medicines administered to the mother**~~	
22.6 Medicines administered to the neonate	
caffeine citrate	**Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL). **Oral liquid:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).
Complementary List	
☐ *ibuprofen* *Therapeutic alternatives:* *– indometacin*	***Solution for injection:** 5 mg/mL.*
☐ *prostaglandin E1* *Therapeutic alternatives:* *– prostaglandin E2*	***Solution for injection:*** 0.5 mg/mL in alcohol.
surfactant	***Suspension for intratracheal instillation:** 25 mg/mL or 80 mg/mL*

23. PERITONEAL DIALYSIS SOLUTION

Complementary List

intraperitoneal dialysis solution (of appropriate composition)	***Parenteral solution.***

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines used in psychotic disorders

Complementary List

chlorpromazine	***Injection:*** *25 mg/mL (hydrochloride) in 2 mL ampoule.* ***Oral liquid:*** *25 mg/5 mL (hydrochloride).* ***Tablet:*** *10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).*
haloperidol	***Injection:*** *5 mg in 1 mL ampoule.* ***Oral liquid:*** *2 mg/mL.* ***Solid oral dosage form:*** *0.5 mg; 2 mg; 5 mg.*

24.2 Medicines used in mood disorders

24.2.1 *Medicines used in depressive disorders*

Complementary List

fluoxetine [a]	***Solid oral dosage form:*** *20 mg (as hydrochloride).* [a] > 8 years.

~~**24.2.2 *Medicines used in bipolar disorders***~~

~~**24.3 Medicines for anxiety disorders**~~

~~**24.4 Medicines used for obsessive compulsive disorders**~~

~~**24.5 Medicines for disorders due to psychoactive substance use**~~

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines

☐ budesonide Therapeutic alternatives: – beclometasone – ciclesonide – flunisolide – fluticasone – mometasone	**Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
☐ salbutamol Therapeutic alternatives: – terbutaline	**Injection:** 50 micrograms/mL (as sulfate) in 5 mL ampoule. **Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose. **Respirator solution for use in nebulizers:** 5 mg/mL (as sulfate).

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**

26.2 Parenteral

glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L).
potassium chloride	**Solution for dilution:** 7.5% (equivalent to K+ 1 mmol/mL and Cl- 1 mmol/mL); 15% (equivalent to K+ 2 mmol/mL and Cl- 2 mmol/mL).
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+167 mmol/L, HCO3- 167 mmol/L). **Solution:** 8.4% in 10 mL ampoule (equivalent to Na+ 1000 mmol/L, HCO3-1000 mmol/L).
sodium lactate, compound solution	**Injectable solution.**

26.3 Miscellaneous

water for injection	2 mL; 5 mL; 10 mL ampoules.

27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.
☐ colecalciferol Therapeutic alternatives: – ergocalciferol	**Oral liquid:** 400 IU/mL. **Solid oral dosage form:** 400 IU; 1000 IU.
iodine	**Capsule:** 190 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
multiple micronutrient powder	**Sachets containing:** – iron (elemental) 12.5 mg (as coated ferrous fumarate) – zinc (elemental) 5 mg – vitamin A 300 micrograms – with or without other micronutrients at recommended daily values
pyridoxine	**Tablet:** 25 mg (hydrochloride).
retinol	**Capsule:** 100 000 IU; 200 000 IU (as palmitate). **Oral oily solution:** 100 000 IU/mL (as palmitate) in multidose dispenser. **Tablet (sugar-coated):** 10 000 IU (as palmitate). **Water-miscible injection:** 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	**Tablet:** 5 mg.
thiamine	**Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:** 100 mg/mL in 10 mL ampoule.*

28. EAR, NOSE AND THROAT MEDICINES

acetic acid	**Topical:** 2%, in alcohol.
☐ budesonide Therapeutic alternatives to be reviewed (2023)	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin Therapeutic alternatives: – ofloxacin	**Solution (ear drops):** 0.3% (as hydrochloride).
☐ xylometazoline [a] Therapeutic alternatives to be reviewed (2023)	**Nasal spray:** 0.05%. [a] Not in children less than 3 months.

29. MEDICINES FOR DISEASES OF JOINTS

~~**29.1 Medicines used to treat gout**~~

29.2 Disease-modifying anti-rheumatic drugs (DMARDs)

Complementary List

hydroxychloroquine	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium salt).*

29.3 Juvenile joint diseases

Complementary List

*acetylsalicylic acid** *(acute or chronic use)*	***Suppository:*** *50 mg to 150 mg.* ***Tablet:*** *100 mg to 500 mg.* * *For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*

30. DENTAL PREPARATIONS

fluoride	**Paste, cream or gel:** containing between 1000 and 1500 ppm fluoride (any type). **In other appropriate topical formulations.**
glass ionomer cement	**Single-use capsules:** 0.4 g powder + 0.09 mL liquid. **Multi-use bottle:** powder + liquid. Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
silver diamine fluoride	**Solution:** 38% w/v.

Annex 3

Alphabetical list of essential medicines (with ATC codes & section numbers)

Medicine or item as in EML	ATC code	Section
abacavir	J05AF06	6.4.2.1
abacavir + lamivudine	J05AR02	6.4.2.5
abiraterone	L02BX03	8.2.4
acetazolamide	S01EC01	21.4
acetic acid	S02AA10	28
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	12.5.1
acetylsalicylic acid	N02BA01	2.1; 7.1; 29.3
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
adalimumab	L04AB04	8.1
albendazole	P02CA03	6.1.1; 6.1.2; 6.1.4
alcohol based hand rub	D08AX08	15.2
allopurinol	M04AA01	8.2.5; 29.1
all-trans retinoid acid (ATRA)	L01XF01	8.2.2
alteplase	B01AD02	12.5.2
amidotriozate	V08AA01	14.2
amikacin	J01GB06	6.2.1; 6.2.5
amiloride	C03DB01	16
amiodarone	C01BD01	12.2
amitriptyline	N06AA09	2.3; 24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amodiaquine – sulfadoxine + pyrimethamine	P01BA06 P01BD51	6.5.3.2
amoxicillin	J01CA04	6.2.1
amoxicillin + clavulanic acid	J01CR02	6.2.1; 6.2.5

Medicine or item as in EML	ATC code	Section
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
anastrozole	L02BG03	8.2.4
anti-D immunoglobulin	J06BB01	11.2.1
anti-rabies immunoglobulin	J06BB05	11.2.1
anti-rabies virus monoclonal antibodies	–	19.2
anti-tetanus immunoglobulin	J06BB02	11.2.1
antivenom immunoglobulin	–	19.2
aprepitant	A04AD12	17.2
arsenic trioxide	L01XX27	8.2.1
artemether	P01BE02	6.5.3.1
artemether + lumefantrine	P01BF01	6.5.3.1
artesunate	P01BE03	6.5.3.1
artesunate + amodiaquine	P01BF03	6.5.3.1
artesunate + mefloquine	P01BF02	6.5.3.1
artesunate + pyronaridine tetraphosphate	P01BF06	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2.1
atazanavir + ritonavir	J05AR23	6.4.2.3
atracurium	M03AC04	20
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	8.1; 29.2
azithromycin	J01FA10	6.2.2
azithromycin	S01AA26	21.1
barium sulfate	V08BA01	14.2
BCG vaccine	L03AX03	19.3
bedaquiline	J04AK05	6.2.5
bendamustine	L01AA09	8.2.1
benzathine benzylpenicillin	J01CE08	6.2.1

Medicine or item as in EML	ATC code	Section
benznidazole	P01CA02	6.5.5.2
benzoyl peroxide	D10AE01	13.4
benzyl benzoate	P03AX01	13.5
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
bevacizumab	S01LA08	21.6
bicalutamide	L02BB03	8.2.4
biperiden	N04AA02	9
bisoprolol	C07AB07	12.1; 12.2; 12.3; 12.4
bleomycin	L01DC01	8.2.1
bortezomib	L01XG01	8.2.2
budesonide	R03BA02	25.1
budesonide	R01AD05	28
budesonide + formoterol	R03AK07	25.1
bupivacaine	N01BB01	1.2
bupropion	N06AX12	24.5
caffeine citrate	N06BC01	22.6
calamine	D02AB	13.3
calcipotriol	D05AX02	13.4
calcium	A12AA20	27
calcium folinate	V03AF03	8.2.1
calcium gluconate	A12AA03	4.2; 27
capecitabine	L01BC06	8.2.1
carbamazepine	N03AF01	5; 24.2.2
carbetocin	H01BB03	22.3
carboplatin	L01XA02	8.2.1
cefalexin	J01DB01	6.2.1
cefazolin	J01DB04	6.2.1
cefiderocol	J01DI04	6.2.3
cefixime	J01DD08	6.2.2
cefotaxime	J01DD01	6.2.2
ceftazidime	J01DD02	6.2.2

Medicine or item as in EML	ATC code	Section
ceftazidime + avibactam	J01DD52	6.2.3
ceftriaxone	J01DD04	6.2.2
cefuroxime	J01DC02	6.2.2
charcoal, activated	A07BA01	4.1
chlorambucil	L01AA02	8.2.1
chloramphenicol	J01BA01	6.2.1
chlorhexidine	D08AC02	15.1; 22.6
chlorine base compound	–	15.2
chloroquine	P01BA01	6.5.3.1; 6.5.3.2; 29.2
chloroxylenol	D08AE05	15.2
chlorpromazine	N05AA01	24.1
cholera vaccine	J07AE	19.3
ciclosporin	L04AD01	8.1
ciprofloxacin	J01MA02	6.2.2
ciprofloxacin	S02AA15	28
cisplatin	L01XA01	8.2.1
clarithromycin	J01FA09	6.2.2
clindamycin	J01FF01	6.2.1
clofazimine	J04BA01	6.2.4; 6.2.5
clomifene	G03GB02	22.2
clomipramine	N06AA04	24.4
clopidogrel	B01AC04	12.5.1
clotrimazole	G01AF02	6.3
cloxacillin	J01CF02	6.2.1
clozapine	N05AH02	24.1
coagulation factor IX	B02BD04	11.2.2
coagulation factor VIII	B02BD02	11.2.2
coal tar	D05AA	13.4
codeine	R05DA04	2.2
colecalciferol	A11CC05	27
colistin	J01XB01	6.2.3
condoms	–	22.1.4

Medicine or item as in EML	ATC code	Section
copper-containing device	G02BA02	22.1.3
cyclizine	R06AE03	2.3
cyclophosphamide	L01AA01	8.2.1
cycloserine	J04AB01	6.2.5
cytarabine	L01BC01	8.2.1
dabigatran	B01AE07	10.2
dacarbazine	L01AX04	8.2.1
daclatasvir	J05AP07	6.4.4.2.1
daclatasvir + sofosbuvir	J05AP07 J05AP08	6.4.4.2.1
dactinomycin	L01DA01	8.2.1
dapsone	J04BA02	6.2.4
darbepoetin alfa	B03XA02	10.1
darunavir	J05AE10	6.4.2.3
dasabuvir	J05AP09	6.4.4.2.2
dasatinib	L01EA02	8.2.2
daunorubicin	L01DB02	8.2.1
deferoxamine	V03AC01	4.2; 10.3
delamanid	J04AK06	6.2.5
dengue vaccine	–	19.3
desmopressin	H01BA02	10.2
dexamethasone	H02AB02	2.3; 3; 8.2.4; 17.2; 22.5
dextran 70	B05AA05	11.3
diaphrams	–	22.1.4
diazepam	N05BA01	2.3; 5; 24.3
diazoxide	V03AH01	18.6
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
dihydroartemisinin + piperaquine phopshate	P01BF05	6.5.3.1
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2

Medicine or item as in EML	ATC code	Section
diphtheria antitoxin	J06AA01	19.2
diphtheria vaccine	J07AF01	19.3
docetaxel	L01CD02	8.2.1
docusate sodium	A06AA02	2.3
dolutegravir	J05AJ03	6.4.2.4
dolutegravir + lamivudine + tenofovir	J05AR27	6.4.2.5
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2.1
doxycycline	J01AA02	6.2.1; 6.5.3.1; 6.5.3.2
efavirenz	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir disoproxil	J05AR06	6.4.2.5
efavirenz + lamivudine + tenofovir disoproxil	J05AR11	6.4.2.5
eflornithine	P01CX03	6.5.5.1
empagliflozin	A10BK03	18.5.2
emtricitabine + tenofovir disoproxil	J05AR03	6.4.2.5
enalapril	C09AA02	12.3; 12.4
enoxaparin	B01AB05	10.2
entecavir	J05AF10	6.4.4.1.1
ephedrine	C01CA26	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 12.2; 25.1
equine rabies immunoglobulin	J06BB05	19.2
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.3
erlotinib	L01EB02	8.2.2
erythromycin	S01AA17	21.1
erythropoiesis-stimulating agents	B03XA01 B03XA02 B03XA03	10.1
estradiol cypionate + medroxyprogesterone acetate	G03AA17	22.1.2

Medicine or item as in EML	ATC code	Section
ethambutol	J04AK02	6.2.5
ethambutol + isoniazid + pyrazinamide + rifampicin	J04AM06	6.2.5
ethambutol + isoniazid + rifampicin	J04AM07	6.2.5
ethanol	D08AX08	15.1
ethinylestradiol + etonogestrel	G02BB01	22.1.6
ethinylestradiol + levonorgestrel	G03AA07	22.1.1
ethinylestradiol + norethisterone	G03AA05	22.1.1
ethionamide	J04AD03	6.2.5
ethosuximide	N03AD01	5
etonogestrel- releasing implant	G03AC08	22.1.5
etoposide	L01CB01	8.2.1
everolimus	L01EG02	8.2.2
fentanyl	N02AB03	2.2
ferrous salt	B03AA02 B03AA07	10.1
ferrous salt + folic acid	B03AD02 B03AD03	10.1
fexinidazole	P01CA03	6.5.5.1
filgrastim	L03AA02	8.2.3
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fludarabine	L01BB05	8.2.1
fludrocortisone	H02AA02	18.1
fluorescein	S01JA01	14.1
fluoride	A01AA	30
fluorouracil	L01BC02	8.2.1; 13.4
fluoxetine	N06AB03	2.3; 24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
fomepizole	V03AB34	4.2
fosfomycin	J01XX01	6.2.3

Medicine or item as in EML	ATC code	Section
fresh frozen plasma	B05AX03	11.1
furosemide	C03CA01	12.4; 16
gemcitabine	L01BC05	8.2.1
gentamicin	J01GB03	6.2.1
gentamicin	S01AA11	21.1
glass ionomer cement	–	30
glecaprevir + pibrentasvir	J05AP57	6.4.4.2.1
gliclazide	A10BB09	18.5.2
glucagon	H04AA01	18.6
glucose	B05CX01	26.2
glucose with sodium chloride	B05BA03	26.2
glutaral	–	15.2
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
Haemophilus influenzae type b vaccine	J07AG01	19.3
haloperidol	N05AD01	2.3; 24.1
halothane	N01AB01	1.1.1
heparin sodium	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
hydralazine	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.2.4; 18.1
hydroxocobalamin	B03BA03	10.1
hydroxycarbamide	L01XX05	8.2.1; 10.3
hydroxychloroquine	P01BA02	29.2
hyoscine butylbromide	A03BB01	2.3
hyoscine hydrobromide	A04AD01	2.3

Medicine or item as in EML	ATC code	Section
ibrutinib	L01EL01	8.2.2
ibuprofen	C01EB16	22.6
ibuprofen	M01AE01	2.1; 7.1
ifosfamide	L01AA06	8.2.1
imatinib	L01EA01	8.2.2
influenza vaccine	J07BB	19.3
insulin injection (soluble) (human)	A10AB01	18.5.1
Intermediate-acting insulin (human)	A10AC01	18.5.1
intraperitoneal dialysis solution	–	23
iodine	H03CA	18.7; 27
iodine	D08AG03	6.3
iohexol	V08AB02	14.2
ipratropium bromide	R03BB01	25.1
irinotecan	L01CE02	8.2.1
isoflurane	N01AB06	1.1.1
isoniazid	J04AC01	6.2.5
isoniazid + pyrazinamide + rifampicin	J04AM05	6.2.5
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	J04AM08	6.4.2.6
isoniazid + rifampicin	J04AM02	6.2.5
isoniazid + rifapentine	J04AC51	6.2.5
isosorbide dinitrate	C01DA08	12.1
itraconazole	J02AC02	6.3
ivermectin	P02CF01	6.1.1; 6.1.2; 6.6
Japanese encephalitis vaccine	J07BA02 J07BA03	19.3
ketamine	N01AX03	1.1.2
lactulose	A06AD11	2.3
lamivudine	J05AF05	6.4.2.1
lamivudine + zidovudine	J05AR01	6.4.2.5

Medicine or item as in EML	ATC code	Section
lamotrigine	N03AX09	5
latanoprost	S01EE01	21.4
ledipasvir + sofosbuvir	J05AP51	6.4.4.2.2
lenalidomide	L04AX04	8.2.3
leuprorelin	L02AE02	8.2.4
levamisole	P02CE01	6.1.1
levodopa + carbidopa	N04BA02	9
levofloxacin	J01MA12	6.2.5
levonorgestrel	G03AC03	22.2.1
levonorgestrel	G03AD01	22.2.1
levonorgestrel-releasing implant	G03AC03	22.1.5
levonorgestrel-releasing intrauterine system	G02BA03	22.1.3
levothyroxine	H03AA01	18.7
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine + epinephrine	N01BB52	1.2
linezolid	J01XX08	6.2.3; 6.2.5
lisinopril + amlodipine	C09BB03	12.3
lisinopril + hydrochlorothiazide	C09BA03	12.3
lithium carbonate	N05AN01	24.2.2
long-acting insulin analogues	A10AE04 A10AE05 A10AE06	18.5.1
loperamide	A07DA03	2.3
lopinavir + ritonavir	J05AR10	6.4.2.3
loratadine	R06AX13	3
lorazepam	N05BA06	5
losartan	C09CA01	12.3; 12.4
Lugol's solution	H03CA	18.7
magnesium sulfate	B05XA05	5
mannitol	B05BC01	16

Medicine or item as in EML	ATC code	Section
measles vaccine	J07BD01	19.3
mebendazole	P02CA01	6.1.1; 6.1.4
medroxyprogesterone acetate	G03AC06	22.1.2
medroxyprogesterone acetate	G03DA02	18.4
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
meglumine iotroxate	V08AC02	14.2
melarsoprol	P01CD01	6.5.5.1
melphalan	L01AA03	8.2.1
meningococcal meningitis vaccine	J07AH	19.3
mercaptopurine	L01BB02	8.2.1
meropenem	J01DH02	6.2.2; 6.2.5
meropenem + vaborbactam	J01DH52	6.2.3
mesna	V03AF01	8.2.5
metformin	A10BA02	18.5.2
methadone	N07BC02	2.2; 24.5
methimazole	H03BB02	18.7
methotrexate	L01BA01	8.2.1
methotrexate	L04AX03	29.2
methyldopa	C02AB01	12.3
methylprednisolone	H02AB04	8.2.4
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	2.3; 17.2
metronidazole	J01XD01	6.2.1
metronidazole	P01AB01	6.5.1
micafungin	J02AX05	6.3
miconazole	D01AC02	13.1
midazolam	N05CD08	1.3; 2.3; 5
mifepristone – misoprostol	G03XB01 G02AD06	22.3
miltefosine	P01CX04	6.5.2
misoprostol	G02AD06	22.3

Medicine or item as in EML	ATC code	Section
morphine	N02AA01	1.3; 2.2
moxifloxacin	J01MA14	6.2.5
multiple micronutrient powder	A11AA01	27
multiple micronutrient supplement	A11AA01	22.5
mumps vaccine	J07BE01	19.3
mupirocin	D06AX09	13.2
naloxone	V03AB15	4.2
natamycin	S01AA10	21.1
neostigmine	N07AA01	20
nevirapine	J05AG01	6.4.2.2
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27
nicotine replacement therapy	N07BA01	24.5
nifedipine	C08CA05	22.4
nifurtimox	P01CC01	6.5.5.1; 6.5.5.2
nilotinib	L01EA03	8.2.2
nitrofurantoin	J01XE01	6.2.1
nitrous oxide	N01AX13	1.1.1
nivolumab	L01FF01	8.2.3
norethisterone enantate	G03AC01	22.1.2
normal immunoglobulin	J06BA	11.2.1
nystatin	A07AA02 G01AA01	6.3
ofloxacin	S01AE01	21.1
ombitasvir + paritaprevir + ritonavir	J05AP53	6.4.4.2.2
omeprazole	A02BC01	17.1
ondansetron	A04AA01	2.3; 17.2
oral rehydration salts	A07CA	17.5.1; 26.1
oral rehydration salts – zinc sulfate	A07CA A12CB01	17.5
oseltamivir	J05AH02	6.4.3

Medicine or item as in EML	ATC code	Section
oxaliplatin	L01XA03	8.2.1
oxamniquine	P02BA02	6.1.3
oxygen	V03AN01	1.1.1; 1.4
oxytocin	H01BB02	22.3
paclitaxel	L01CD01	8.2.1
p-aminosalicylic acid	J04AA01	6.2.5
pancreatic enzymes	A09AA02	17
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
pegaspargase	L01XX24	8.2.1
pegylated interferon alfa (2a or 2b)	L03AB10 L03AB11	6.4.4.2.3
penicillamine	M01CC01	4.2; 29.2
pentamidine	P01CX01	6.5.4; 6.5.5.1
permethrin	P03AC04	13.5
pertussis vaccine	J07AJ01	19.3
phenobarbital	N03AA02	5
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
piperacillin + tazobactam	J01CR05	6.2.2
platelets	B05A	11.1
plazomicin	J01GB14	6.2.3
pneumococcal vaccine	J07AL01	19.3
podophyllum resin	--	13.4
poliomyelitis vaccine	J07BF	19.3
polymyxin B	J01XB02	6.2.3
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II) $\cdot 2H_2O$ (Prussian blue)	V03AB31	4.2
potassium iodide	D08AG03	6.3

Medicine or item as in EML	ATC code	Section
potassium iodide	V03AB21	18.7
potassium permanganate	D08AX06	13.2
povidone iodine	D08AG02	15.1
praziquantel	P02BA01	6.1.1; 6.1.3; 6.1.4
prednisolone	H02AB06	3; 8.2.4
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1
procaine benzylpenicillin	J01CE09	6.2.1
procarbazine	L01XB01	8.2.1
progesterone vaginal ring	G02BB02	22.1.6
proguanil	P01BB01	6.5.3.2
propofol	N01AX10	1.1.2
propranolol	C07AA05	7.2
propylthiouracil	H03BA02	18.7
prostaglandin E1	C01EA	22.6
protamine sulfate	V03AB14	10.2
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.5
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
quinine	P01BC01	6.5.3.1
rabies vaccine	J07BG	19.3
raltegravir	J05AJ01	6.4.2.4
ranitidine	A02BA02	17.1
rasburicase	V03AF07	8.2.5
realgar-Indigo naturalis formula	–	8.2.1
red blood cells	B05AX01	11.1
retinol	A11CA01	27
ribavirin	J05AP01	6.4.3; 6.4.4.2.3
riboflavin	A11HA04	27

Medicine or item as in EML	ATC code	Section
rifabutin	J04AB04	6.2.5
rifampicin	J04AB02	6.2.4; 6.2.5
rifapentine	J04AB05	6.2.5
risperidone	N05AX08	24.1
ritonavir	J05AE03	6.4.2.3
rituximab	L01FA01	8.2.2
rotavirus vaccines	J07BH	19.3
rubella vaccines	J07BJ	19.3
salbutamol	R03AC02	25.1
salicylic acid	D01AE12	13.4
selenium sulfide	D01AE13	13.1
senna	A06AB06	2.3; 17.4
silver diamine fluoride	–	30
silver sulfadiazine	D06BA01	13.2
simvastatin	C10AA01	12.6
sodium calcium edetate	V03AB03	4.2
sodium chloride	B05XA03	26.2
sodium hydrogen carbonate	B05XA02	26.2
sodium lactate compound solution	–	26.2
sodium nitrite	V03AB08	4.2
sodium nitroprusside	C02DD01	12.3
sodium stibogluconate	P01CB02	6.5.2
sodium thiosulfate	V03AB06	4.2; 13.1
sofosbuvir	J05AP08	6.4.4.2.1
sofosbuvir + velpatasvir	J05AP55	6.4.4.2.1
spectinomycin	J01XX04	6.2.1
spironolactone	C03DA01	12.4; 16
streptokinase	B01AD01	12.5.2
streptomycin	J01GA01	6.2.5
succimer	–	4.2
sulfadiazine	J01EC02	6.5.4
sulfadoxine + pyrimethamine	P01BD51	6.5.3.1

Medicine or item as in EML	ATC code	Section
sulfamethoxazole + trimethoprim	J01EE01	6.2.1; 6.5.4
sulfasalazine	A07EC01	17.3; 29.2
sumatriptan	N02CC01	7.1
suramin sodium	P01CX02	6.5.5.1
suxamethonium	M03AB01	20
tacrolimus	L04AD02	8.1
tamoxifen	L02BA01	8.2.4
telmisartan + amlodipine	C09DB04	12.3
telmisartan + hydrochlorothiazide	C09DA07	12.3
tenofovir disoproxil fumarate	J05AF07	6.4.2.1; 6.4.4.1.1
terbinafine	D01AE15	13.1
testosterone	G03BA03	18.2
tetanus vaccine	J07AM01	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thalidomide	L04AX02	8.2.3
thiamine	A11DA01	27
tick-borne encephalitis vaccine	J07BA01	19.3
timolol	S01ED01	21.4
tioguanine	L01BB03	8.2.1
tiotropium	R03BB04	25.1
tranexamic acid	B02AA02	10.2; 22.5
trastuzumab	L01FD01	8.2.2
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.1
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD)	V04CF01	19.1
typhoid vaccine	J07AP	19.3
ulipristal	G03AD02	22.1.1
urea	D02AE01	13.4

Medicine or item as in EML	ATC code	Section
valganciclovir	J05AB14	6.4.3
valproic acid (sodium valproate)	N03AG01	5; 24.2.2
vancomycin	J01XA01 A07AA09	6.2.2
varenicline	N07BA03	24.5
varicella vaccines	J07BK	19.3
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2
vinblastine	L01CA01	8.2.1
vincristine	L01CA02	8.2.1
vinorelbine	L01CA04	8.2.1
voriconazole	J02AC03	6.3
warfarin	B01AA03	10.2
water for Injection	V07AB	26.3
whole blood	B05A	11.1
xylometazoline	R01AA07	28
yellow fever vaccine	J07BL01	19.3
zidovudine	J05AF01	6.4.2.1
zinc sulfate	A12CB01	17.5.2
zoledronic acid	M05BA08	8.2.5

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This report presents the recommendations of the WHO Expert Committee responsible for updating the Who Model List of Essential Medicines and WHO Model List of Essential Medicines for Children. It contains a summary of the evidence presented and the Committee's consideration, justifications and recommendations for additions, deletions and changes to medicines on the Model Lists.

Annexes to the main report include the WHO Model List of Essential Medicines – 22nd list (2021), the WHO Model List of Essential Medicines for Children – 8th list (2021), and the list of all essential medicines with Anatomical Therapeutic Chemical (ATC) classification codes.

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