Executive summary
The Selection and Use of Essential Medicines 2021

Report of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines

Virtual meeting, 21 June–2 July 2021

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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 3 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 and 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 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 timeframes. 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 7 to the complementary list);
- recommended the addition of 17 new medicines to the EMLc (12 to the core list and 5 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 2 medicines and of specific formulations of a further 13 medicines;
- updated 72 square box listings, removed the square box from 7 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

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

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 multi-drug 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 microbiologic/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 intraabdominal 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 multi-drug 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 TB preventive treatment (TPT, previously known as treatment for latent tuberculosis infection (LTBI)), to reduce pill burden and improve treatment adherence to WHO-recommended TPT 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 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, and 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, that 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 to 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 for 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 of rescue medication use. Compared to 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 to 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 four to six 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, who 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 (SEGA) 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, improving control of resulting disorders (seizures, developmental delays). The Expert Committee did not endorse the use of everolimus for indications other than SEGA.
- 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 chemo-immunotherapy. The Committee noted that targeted therapy with ibrutinib, is replacing chemo-immunotherapy 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 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 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 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 to 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 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 / 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 regarding optimal dose and duration of therapy, 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, 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 to 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, together with 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 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 to 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 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 NSCLC 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 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 for 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's 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 to other EML listed medicines for CLL 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.

<u>Review of evidence for CAR-T therapy for diffuse large B-cell lymphoma</u>

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 (DLBCL). 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 what is 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 DLBCL, 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 that calcipotriol is effective compared to placebo, but not superior to topical corticosteroids. It has a favourable safety profile compared to 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: (RE-NAMED) 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 clarify 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 (PCOS). The Committee considered that while the available evidence suggests simvastatin is associated with improvements in biochemical markers in patients with PCOS, there was inadequate evidence of for 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 PCOS mainly affects

reproductive-aged women and one aim of treatment of PCOS 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 (RE-NAMED) 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 post-exposure prophylaxis (PEP), 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 PEP 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 to 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 to 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 has considered methylphenidate, following a recommendation not to include it in 2019 due to uncertainties in the estimates of benefit, and concerns regarding 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 a relatively large symptom reductions in the 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 be of 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 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 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 the 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 anti-psychotics 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 country level, together with strengthening of national tobacco control policies.

Section 29: Medicines for diseases of joints

Section 29.2 (RE-NAMED) 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 ophthalmologic monitoring should 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 systemic onset juvenile idiopathic arthritis (SOJIA) with macrophage activation syndrome (MAS), nor tocilizumab for the treatment of children with SOJIA because of because uncertainty in the estimates of clinical benefits, as well as concerns about access and affordability across 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 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 to 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 re-named "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, 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 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;
- 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 (MPP) 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 MPP'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 MPP 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 (CDK) 4/6 inhibitors, daratumumab, osimertinib, PD-1/PD-L1 immune checkpoint inhibitors and zanubrutinib all had potential for future inclusion and recommended the MPP 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 anti-tumour necrosis factor (TNF) biologics, erythropoietins and insulins. The Committee noted that a substantial body of evidence exists that the switch from originators to biosimilars 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 with regard to biosimilars and not the pharmacologic 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 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 country level for national essential medicines lists. The Committee recognized that considerable heterogeneity exists in the Model Lists with the use and application of the 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 4th 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 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 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 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 7 as Reserve), and will be included in the 2021 update of the AWaRe classification database.

The Committee also noted the request from the WHO AMR Global Coordination Department for a comprehensive review of 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 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 post-exposure prophylaxis	Anti-rabies virus monoclonal antibodies	Rabies post-exposure prophylaxis
Bupropion	Smoking cessation	□ Calcipotriol	Psoriasis
□ Calcipotriol	Psoriasis	Daclatasvir	Hepatitis C
Cefiderocol	Infection due to multi-drug resistant pathogens	Daclatasvir + sofosbuvir	Hepatitis C
□ Empagliflozin	Type 2 diabetes mellitus	Equine rabies immunoglobulin	Rabies post-exposure prophylaxis
Equine rabies immunoglobulin	Rabies post-exposure 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
Hydroxychloroquine	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
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 intraabdominal 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
Cyclophosphamide	Low-grade glioma, nephroblastoma	Clindamycin	Necrotizing fasciitis
Dactinomycin	Ewing sarcoma	Cyclophosphamide	Low-grade glioma, nephroblastoma
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 intraabdominal 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
Methylprednisolone	Burkitt lymphoma	Mesna	Burkitt lymphoma, nephroblastoma
Metronidazole	Necrotizing fasciitis	Methotrexate	Burkitt lymphoma
Moxifloxacin	Drug-susceptible tuberculosis	Methylprednisolone	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
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	Cyclophosphamide	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
Cyclophosphamide	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)/2mL
Isoniazid + rifapentine	Tablet (scored): 300 mg + 300 mg		
Phenoxymethylpenicillin	Tablet: 500 mg		
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)/2mL		
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
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
6.2.1	Cloxacillin	4th 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	4th 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	4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives)	EML
12.3	Enalapril	4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)	EML & EMLc
12.3	Hydrochlorothiazide	Chlorothiazide, chlorthalidone, indapamide	EML
12.3	Lisinopril + amlodipine	4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril component) 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine component)	EML
12.3	Lisinopril + hydrochlorothiazide	4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril component) Indapamide, chlorthalidone, chlorothiazide (for hydrochlorothiazide component)	EML
12.3	Losartan	4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	EML
12.3	Telmisartan + amlodipine	4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan component) 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine component)	EML

12.3	Telmisartan + hydrochlorothiazide	4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan component) Indapamide, chlorthalidone, chlorothiazide (for hydrochlorothiazide component)	EML
12.4	Enalapril	4th 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	4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	EML
12.6	Simvastatin	Atorvastatin, fluvastatin, lovastatin, pravastatin	EML
13.1	Miconazole	4th level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	EML & EMLc
13.3	Betamethasone	4th level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	EML & EMLc
13.3	Calamine	Remove square box	EML
13.3	Hydrocortisone	4th 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	4th level ATC chemical subgroup (D08AE Phenol and derivatives)	EML & EMLc
16	Furosemide	4th 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	4th level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	EML & EMLc
17.1	Ranitidine	4th level ATC chemical subgroup (A02BA H_2-receptor antagonists) excluding combinations	EML & EMLc
17.2	Ondansetron	Dolasetron, granisetron, palonosetron, tropisetron	EML & EMLc
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	4th level ATC chemical subgroup (A10BB Sulfonylureas)	EML
21.1	Gentamicin	Amikacin, kanamycin, netilmicin, tobramycin	EML & EMLc
21.1	Ofloxacin	4th level ATC chemical subgroup (S01AE Fluoroquinolones)	EML & EMLc
21.1	Tetracycline	Chlortetracycline, oxytetracycline	EML & EMLc
21.3	Tetracaine	4th level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	EML & EMLc
21.4	Pilocarpine	Carbachol	EML
21.4	Timolol	4th 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
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
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 sub-sections 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
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

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 (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 at 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, the Netherlands

Verna Vanderpuye, Clinical oncologist, senior consultant, National Centre for Radiotherapy, Oncology and Nuclear Medicine, Korle-Bu 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 Paediatrics and Director of the Paediatric 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

UN 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

WHO Regional Office for the Americas / Pan American Health Organization

Jose Luis Castro, Advisor, Essential Medicines and Biologicals, Washington DC, United States of America

Edgard Robin Rojas Cortes, Technical Officer, Safe Use of Medicines, Washington DC, United States of America

WHO Regional Office for the Eastern Mediterranean

Adi Al-Nuseirat, Technical Officer, Access to Pharmaceuticals, Cairo, Egypt

WHO Regional Office for South-East Asia

Uhjin Kim, Technical Officer, Essential Drugs and Medicines, New Delhi, India

WHO Headquarters Geneva - Secretariat

Benedikt Huttner, Secretary of the Expert Committee on Selection and Use of Essential Medicines, Department of Health Products Policy and Standards, Access to Medicines and Health Products

Bernadette Cappello, Technical Officer, EML Secretariat, Department of Health Products Policy and Standards, Access to Medicines and Health Products

Albert Figueras, Consultant, EML Secretariat, Department of Health Products Policy and Standards, Access to Medicines and Health Products

Lorenzo Moja, Scientist, EML Secretariat, Department of Health Products Policy and Standards, Access to Medicines and Health Products

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

Declaration of Interests

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 program 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 (HIPEC) 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 program (National Surgical Adjuvant Breast and Colon Project) and a for-profit company (Daiichi Sankyo). Trial sponsors provide funding to her institution, 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 (University Medical Center Groningen) is involved in early phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers. Her institution receives research support funding from Amgen, Bayer, CytomX, Crescendo Biologics, Genentech, G1 Therapeutics, Regeneron, Roche, Servier and Synthon. These trials are considered to not 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 to not be directly related to the subject matter of the Expert Committee meeting and were determined 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, 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 (MPP), a non-State actor in official relations with WHO. She remains a member of the expert advisory group of the MPP. She disclosed having received grant funding from UNITAID to conduct a summary review on access to COVID-19 related health products. These disclosures were judged to be not directly related to the subject matter of the Expert Committee meeting and were determined 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 drug (venetoclax and ibrutinib, respectively) for trials in mantle cell lymphoma. Servier provided financial support for laboratory-based research on B-cell lymphoma-2 (BCL2) 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 WEHI and the pharmaceutical companies AbbVie and Genentech. AbbVie and Genentech are responsible for the commercial development of venetoclax. WEHI has no role in its clinical trial development, commercialization or marketing. WEHI 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 outcome of clinical trials, nor future drug sales. In 2017, WEHI 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 pre-date 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 judgment 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 for use in adults at this meeting. 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 not considered non-significant and determined not to represent a conflict.

He also disclosed that he served as co-Principal Investigator for a phase 2 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 Fondazione's research units 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 license 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 on the EML at this time, and a recommendation to list 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 donation of drug from Sun Pharmaceutical Industries Limited. This activity not associated with 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.