The selection and use of essential medicines 2023

Executive summary of the report of the 24th WHO Expert Committee on Selection and Use of Essential Medicines

24 – 28 April 2023

World Health Organization

The selection and use of essential medicines 2023

Executive summary of the report of the 24th WHO Expert Committee on Selection and Use of Essential Medicines

24 – 28 April 2023

WHO/MHP/HPS/EML/2023.01

Contents

Web annexes

Web Annex A. WHO Model List of Essential Medicines, 23rd List (2023)
https://apps.who.int/iris/bitstream/handle/10665/371090/WHO-MHP-HPS-EML-2023.02-eng.pdf

Web Annex B. WHO Model List of Essential Medicines for Children, 9th List (2023)
https://apps.who.int/iris/bitstream/handle/10665/371091/WHO-MHP-HPS-EML-2023.03-eng.pdf

Web Annex C. WHO AWaRe (access, watch, reserve) classification of antibiotics for evaluation and monitoring of use.
https://apps.who.int/iris/bitstream/handle/10665/371093/WHO-MHP-HPS-EML-2023.04-eng.xlsx

Acknowledgements

WHO gratefully acknowledges the significant contributions of the Expert Committee members and temporary advisers who participated in the meeting of the 24th WHO Expert Committee on Selection and Use of Essential Medicines.

List of participants

Committee Members

Loice Achieng Ombajo, Infectious disease specialist, and senior lecturer at the University of Nairobi Department of Medicine, Nairobi, Kenya.

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).*

Francesco Ceppi, Staff physician in Paediatric Oncology/Haematology, University Hospital CHUV, Lausanne, Switzerland.

Abdol Majid Cheraghali, Professor of Pharmacology, Faculty of Pharmacy, BMS University, Tehran, the Islamic Republic of Iran.

Pem Chuki, Assistant Professor of Medicine, Jigme Dorji Wangchuck National Hospital, Thimphu, Bhutan.

Carlos Alberto Cuello Garcia, Assistant Professor, Department of Health Research Methods, Evidence, and Impact, McMaster University, Canada; Professor in Evidence-Based Healthcare Quality Improvement at the Tecnologico de Monterrey School of Medicine, Mexico.

Elisabeth de Vries, Professor of Medical Oncology, University Medical Center, Groningen, Netherlands (Kingdom of the).

Wei Hao, Professor of Psychiatry and Director of the WHO Collaborating Centre for Psychosocial Factors, Substance Abuse and Health, Central South University, Changsha, China.

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

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

Mike Sharland, Professor of Paediatric Infectious Diseases, St George's University, London, United Kingdom of Great Britain and Northern Ireland *(Co-chair).*

Sangeeta Sharma, Professor of Neuropsychopharmacology, Institute of Human Behaviour and Allied Sciences, Delhi, India.

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

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

Temporary advisers

Elie Akl, Professor of Medicine and Associate Dean for Clinical Research, American University of Beiruit, Beiruit, Lebanon.

Claudia Garcia Serpa Osorio de Castro, Professor and Senior Researcher, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil.

Ilisabeta Pesamino, Chief Pharmacist, Fiji Ministry of Health and Medical Services and Fiji Medicines Regulatory Authority, Suva, Fiji.

Zoubida Tazi Mezalek, Professor of Internal Medicine and Head of the Clinical Hematology Department, University of Rabat, Rabat, Morocco.

UN Agencies

United Nations Children's Fund (UNICEF)

Mary Ojoo, Technical Manager, Medicines and Nutrition Center, UNICEF Supply Division, Copenhagen, Denmark.

WHO regional offices

Region of the Americas

Hector Eduardo Castro Jaramillo, Unit Chief, Medicines and Health Technologies, Department of Health Systems and Services, Washington DC, United States of America.

South-East Asia Region

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

Eastern Mediterranean Region

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

WHO headquarters Geneva - Secretariat

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

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

Kristina Jenei, Temporary Adviser, EML Secretariat, Department of Health Product Policy and Standards, Access to Medicines and Health Products.

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

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

Declaration of Interests

To be effective, the work of WHO and the contributions of its experts must be, and must be perceived to be, objective and independent. In this regard, to ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential or reasonably perceived conflict of interest related to the subject of the activity in which they will be involved. Declarations of interest and management of any disclosures is an important process governed by the WHO Guidelines for Declaration of Interests (WHO Experts). More information regarding WHO's policy on declarations of interest is available on the WHO website[1].

Prior to being invited to participate in the 24th meeting of the WHO Expert Committee on Selection and Use of Essential Medicines, all experts submitted written declarations of interest. 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 Elie Akl, Zeba Aziz, Francesco Ceppi, Abdol Majid Cheraghali, Pem Chuki, Patrick Okwen, Ilisabeta Pesamino, Gabriela Prutsky-Lopez, Sangeeta Sharma, Fatima Suleman and Indah Widyahening.

The following experts disclosed interests, which were assessed by the Secretariat for actual or potential conflicts and management strategies (if required):

Loice Achieng Ombajo disclosed receiving honoraria from GSK to serve on a scientific advisory board for the Africa Open Lab research programme, from ViiV Healthcare to serve on a scientific advisory board on HIV and Aging, and from Astra Zeneca to serve on a COVID-19 advisory board. She also disclosed having received honoraria from Astra Zeneca, Merck Sharp and Dohme and Mylan Laboratories for speaker engagements and conference travel on topics not related to medicines under evaluation at this meeting. All payments were below the threshold of significant financial interest. Dr Achieng Ombajo also disclosed funding to her institution (University of Nairobi) from ViiV Healthcare and Gilead Sciences for investigator-initiated clinical trials on medicines for HIV (not under evaluation at this meeting), for which she is the principal investigator. Dr Ombajo is the clinical lead of two country grant programs, the first to improve surveillance of *Candida auris* in Kenya (funded by the Centers for Diseases Control and Prevention) and the second to improve antimicrobial surveillance (funded by the Fleming Fund). These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Rita Banzi disclosed research funding to her research unit and institution (Mario Negri Institute for Pharmaceutical Research) below the threshold of significant financial interest from Janssen Pharmaceuticals to support an educational programme for systematic review methodology. She also disclosed funding to her research unit and institution from AC.TA .s.r.l. to support a series of ongoing investigator-initiated clinical trials on the use of hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of different cancers. No personal salary support was received. These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Carlos Alberto Cuello Garcia disclosed an appointment as senior research officer by the Canadian Agency for Drugs and Technology in Health (CADTH). In this capacity Dr Cuello prepares evaluations of medicines that are

[1] https://www.who.int/about/ethics/declarations-of-interest

presented to Agency's policymakers to make reimbursement decisions. This disclosure was considered not to represent a conflict and did not require further management.

Elisabeth de Vries disclosed that she serves as an expert in data safety monitoring committees for an ongoing trial investigating atezolizumab in adjuvant breast cancer sponsored by a non-profit research program (National Surgical Adjuvant Breast and Colon Project) and for a completed trial investigating trastuzumab deruxtecan in advanced breast cancer sponsored by a for-profit company (Daiichi Sankyo). Dr de Vries also disclosed that she provides advice to Crescendo Biologics on improving the quality of the design and conduct of preclinical and phase I clinical studies exploring biological activity of bispecific molecules for the treatment of cancers. Sponsors provide funding to Dr de Vries' institution (University Medical Center Groningen) to cover her time commitment.

She also disclosed that her institution is involved in early phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers. Her institution receives institutional funding from Amgen, Bayer, CytomX, Crescendo Biologics, Genetech, G1 Therapeutics, Regeneron, Roche, Servier and Synthon. No personal salary support was received. The trials concerned were not considered to be directly related to medicines under evaluation at the Expert Committee meeting.

She disclosed that she is a current member of the European Society for Medical Oncology Magnitude of Clinical Benefit Scale Working Group, having served as its Chair from 2013 to 2019, and is a current member of the Response Evaluation Criteria in Solid Tumours Working Group, having been its co-chair from 2009 to 2022. She has served as the Chair of the EML Cancer Medicines Working Group since 2020 and was involved in the Working Group's evaluation of cancer medicine applications under consideration at the Expert Committee meeting. All these positions are unpaid.

These disclosures were considered to be unrelated, or not directly related, to the subject matter of the Expert Committee meeting and did not require further management.

Wei Hao disclosed that was the principal investigator of a phase II clinical trial evaluating a long-acting naltrexone implant to treat opioid dependence sponsored by Shenzhen Sciencare Medical Industries. He disclosed having received honoraria in relation to the conduct of the trial, below the threshold for significant financial interest. The sponsors provided funding to Dr Hao' institution (Second Xiangya Hospital, Central South University) to cover trial costs. Naltrexone (oral formulation and extended-release injection) is a medicine under evaluation at the Expert Committee meeting for treatment of alcohol use disorder. This disclosure was considered to represent an ostensible conflict of interest. A determination was made that he should be excluded from the deliberation and recommendation for the application for naltrexone. He recused himself from the meeting while the application for naltrexone was being discussed.

Claudia Garcia Serpa Osorio de Castro disclosed that she has received grant funding for consultancy work from Oswaldo Cruz Foundation Funding Agency to support a project on litigation for access to high-cost medicines sponsored by the Brazilian Ministry of Health, and research grant funding from the National Council for Scientific and Technological Development, a foundation linked to the Brazilian Ministry of Science and Technology, to support masters and PhD students involved in comparative effectiveness research. These disclosures were considered not to represent a conflict and did not require further management.

Mike Sharland disclosed that his institution (St George's University of London) has received research funding from GARDP to support the development of academic activities, including observational cohort studies, and monitoring antibiotic use in children. GARDP is funded exclusively from independent, non-commercial sources. He also disclosed that he is the Vice Chair and Board Member of the Penta Foundation, an Italian

Charitable Foundation, that globally supports trials to advance treatments for pediatric infectious diseases. Penta collaborates with multiple drug companies on the optimal design and conduct of observational and interventional trials of medicines. He has served as the Chair of the EML Antimicrobials Working Group since 2017 and was involved in the Working Group's evaluation of antibiotic applications under consideration at the Expert Committee meeting. Both positions are unpaid. These disclosures were considered not to represent a conflict and did not require further management.

He also disclosed that he is the chief investigator of the ongoing PediCAP trial, an EU-funded study, comparing amoxicillin to amoxicillin + clavulanic acid in children admitted to hospital with severe pneumonia in Africa. Sandoz is donating amoxicillin + clavulanic dispersible tablets for the trial. He also disclosed that he is the chief investigator of the NeoSEP1 trial, funded by the Global Antibiotic Research and Development Partnership (GARDP) and the European & Developing Countries Clinical Trials Partnership (EDCTP), which compares novel combinations of generic antibiotics to treat neonatal sepsis. The antibiotics under study include fosfomycin, provided by InfectoPharm, and flomoxef, provided by Shionogi & Co. Both positions are unpaid. Applications for amoxicillin + clavulanic acid dispersible tablets (submitted by Sandoz) and flomoxef (submitted by GARDP) were under evaluation at the Expert Committee meeting. These disclosures were considered to represent an ostensible conflict of interest. A determination was made that he should be excluded from the deliberation and recommendation for the applications for amoxicillin + clavulanic acid dispersible tablets and flomoxef. He recused himself from the meeting while these applications were being discussed.

Zoubida Tazi Mezalek disclosed financial support below the threshold for significant financial interest from pharmaceutical companies (Hikma, Janssen, AfricPhar, and Health Innovation) for reimbursement of travel and accommodation expenses for attendance at conferences. She also disclosed that she served as an investigator in an observational study sponsored by Servier and a phase IV study sponsored by Roche. These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Executive summary

The meeting of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines took place in person in Geneva, Switzerland, from 24 to 28 April 2023. The aim of the meeting was to review and update the 22nd WHO Model List of Essential Medicines (EML) and the 8th WHO Model List of Essential Medicines for Children (EMLc) (the "Model Lists").

Essential medicines are those that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford.

The WHO Model Lists are updated every two years, intended as a guide for countries or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines for the development and updating of national essential medicines lists. Selection of a limited number of essential medicines as essential, taking into consideration national disease burden and clinical need can lead to improved access through streamlined procurement and distribution of quality-assured medicines, support more rational or appropriate prescribing and use and lower costs for both health care systems and for patients.

The Expert Committee considered a total of 85 applications, including 52 proposals for the addition of new medicines or medicine classes, 9 proposals for new indications for 22 currently listed medicines, 9 proposals for the addition of new formulations of currently listed medicines, and 6 proposals for the removal of 13 medicines, formulations or indications, and 9 proposals for other changes to current listings on the Model Lists. In accordance with applicable procedures[2], the Expert Committee reviewed and evaluated the scientific evidence for the effectiveness, safety and comparative cost-effectiveness of the medicines in question. The Committee also considered a review of the age-appropriateness of formulations of essential medicines for children on the EMLc.

In summary, the Expert Committee:

- recommended the addition of 24 new medicines to the EML (15 to the core list and 9 to the complementary list);
- recommended the addition of 12 new medicines to the EMLc (8 to the core list and 4 to the complementary list);
- recommended adding additional indications for 16 currently listed medicines;
- recommended the addition of new formulations of 19 medicines on the EML and of 48 medicines on the EMLc;
- recommended the deletion of 3 medicines from the EML and 3 medicines from the EMLc and of specific formulations of a further 12 medicines from the EML and 23 medicines from the EMLc; and
- did not recommend proposals for inclusion, change or deletion for 32 medicines, medicine classes or formulations.

The recommended changes bring the total number of medicines (including fixed-dose combinations) on the EML to 502 (from 479 in 2021), including 361 on the EMLc (from 350 in 2021).

[2] https://apps.who.int/gb/ebwha/pdf_files/EB109/eeb1098.pdf

Changes to the Model Lists are shown in Tables 1 – 3. Applications for proposed changes to the Model Lists that were not recommended are shown in Table 4.

The Expert Committee's recommendations are briefly described in this document.

The WHO Model List of Essential Medicines, 23rd list (2023), is available at Web Annex A. The WHO Model List of Essential Medicines List for Children, 9th list (2023) is available at Web Annex B.

Section 1: Anaesthetics, preoperative medicines and medical gases

Section 1.1.1 Inhalational medicines

The Expert Committee recommended the inclusion of sevoflurane as an inhalational anaesthetic on the core list EML and EMLc based on evidence of similar efficacy and safety to currently listed isoflurane. The Committee noted that sevoflurane has a lower global warming potential than other volatile anaesthetics, particularly desflurane, which is not listed as an essential medicine, but also halothane and isoflurane, which are both currently included. More efficient use of sevoflurane, in preference to other inhalational anaesthetics, can contribute to reducing greenhouse gas emissions and the environmental impact of climate change.

Section 2: Medicines for pain and palliative care

Section 2.2 Opioid analgesics

The Expert Committee did not recommend the inclusion of fast-acting oral transmucosal formulations of fentanyl citrate on the EML for the treatment of breakthrough cancer pain based on significant incremental costs compared to immediate-release oral morphine, which were considered disproportionate to the marginal incremental benefits. The Committee also noted that fentanyl has much higher potency and more drug-interactions than other opioids, which limit its manageability. The Committee was also concerned that transmucosal fentanyl formulations have greater potential for misuse and addiction.

Section 5: (re-named) Medicines for diseases of the nervous system

This section of the Model Lists has been re-named from “Anticonvulsants/antiepileptics” to “Medicines for diseases of the nervous system” and includes new sub-sections for antiseizure medicines, medicines for multiple sclerosis, and medicines for parkinsonism (formerly listed in Section 9).

The Expert Committee did not recommend inclusion of donepezil on the EML for the treatment of dementia due to Alzheimer disease. The Committee noted that moderate certainty evidence suggested donepezil may be associated with short-term improvements on cognitive outcome scores compared with placebo. However, these improvements are unlikely to be clinically meaningful. The Committee noted that the evidence suggests that the effect on activities of daily living is limited, while the available evidence suggests no impact on behavioural symptoms and quality of life, and lack of longer-term clinical cognitive benefits. The Committee noted that adverse effects of donepezil are generally mild, but the risk increases with higher doses, (those associated with greater cognitive benefits in the short-term), and the potential for numerous drug-drug and drug-disease interactions. The Committee considered that the patients included in dementia trials are generally younger and characterized by a better performance than patients seen in routine dementia care, affecting the generalizability of trial results. Consequently, the Committee considered the overall benefit to harm profile of the medicine to be unfavourable.

The Expert Committee did not recommend inclusion of risdiplam on the core list of the EML and EMLc for treatment of spinal muscular atrophy. The Committee noted that the body of evidence for efficacy and safety of risdiplam in spinal muscular atrophy is still limited, with only a small number of patients exposed to long-term treatment. The Committee, therefore, considered that the overall magnitude and long-term duration of benefits and potential harms were still uncertain. The Committee noted that based on the available evidence in patients with symptomatic disease, improvements in motor function were observed in younger children (below 5 years) but that these improvements became increasingly less prominent in older children, adolescents and adults. The Committee took note of ongoing clinical trials of risdiplam in presymptomatic infants up to 6 weeks of age and the introduction of routine newborn screening for spinal muscular atrophy

in some settings and considered that the outcomes of these trials and screening programmes would be informative for future consideration of risdiplam for inclusion on the Model Lists.

Section 5.1 (new sub-section) Antiseizure medicines

The Expert Committee recommended the inclusion of oral levetiracetam on the core list of the EML and EMLc for the treatment of focal-onset and generalized-onset seizures in adults in children. The Committee also recommended the inclusion of parenteral levetiracetam on the complementary list of the EML and EMLc for use in the management of benzodiazepine-refractory status epilepticus. These recommendations were made based on evidence of effectiveness and safety, and in recognition of the need for treatment strategies for people with epilepsy to be individualized taking into account multiple factors including, but not limited to, pregnancy and patient preferences, seizure type, co-morbidities, and concomitant use of other medications. These recommendations are also aligned with expected recommendations in the updated WHO Mental Health Gap Action Programme (mhGAP) guidelines.

Section 5.2 (new sub-section) Medicines for multiple sclerosis

The Expert Committee recommended the inclusion of cladribine, glatiramer acetate and rituximab as individual medicines on the complementary list of the EML for the treatment of multiple sclerosis. The Committee did not recommend the inclusion of ocrelizumab for this indication, either as an individual medicine, or as a therapeutic alternative to rituximab under a square-box listing.

The Committee noted that multiple sclerosis is the most common non-traumatic cause of neurological disability in young adults, with approximately 2.8 million people living with multiple sclerosis worldwide. Until now, the EML has not included any medicines for the treatment of multiple sclerosis. The Committee considered that the inclusion of effective and safe treatments for multiple sclerosis on the EML would address an important public health need and support global advocacy efforts to reduce the global burden of multiple sclerosis, especially in low and middle-income countries.

The Committee acknowledged the availability of a large number of disease-modifying medicines for multiple sclerosis (particularly for the treatment of relapsing and remitting forms of the disease) and the need to prioritize the most effective, tolerable, and affordable options. The Committee considered that the approach taken in the application submitted by the Multiple Sclerosis International Federation (MSIF) to identify which medicines to prioritize for EML listing from among the many available was comprehensive, up-to-date, transparent, robust and evidence based. The Committee recognized the value of involving different organizations and stakeholders at the global level, including consultation with people living with multiple sclerosis. The Committee considered that the application's selection of cladribine, glatiramer acetate and rituximab as priority medicines for EML inclusion was well justified and supported by evidence of clinical benefit and safety across different settings, as well as suitability for use in different patient populations (e.g. pregnant women) and feasibility. The inclusion on the EML of three medicines, with different routes of administration, different prices (including the availability of generics and biosimilars) and different recommended uses, would provide valuable options for patients and national selection decisions and could facilitate improved access to treatment for people living with multiple sclerosis. The Committee acknowledged that rituximab does not have market authorization by regulatory authorities for treatment of multiple sclerosis and is thus used "off-label" for this indication. The Committee reiterated that the Model List can play an important role identifying those medicines for which off-label use is supported by convincing evidence, complementing the assessment and labeling by jurisdictional authorities.

The Committee acknowledged the benefits of ocrelizumab in the management of relapsing and primary progressive forms of multiple sclerosis. However, there was no compelling evidence of its superiority over

other alternatives, specifically rituximab, which has the same target (CD20) and a similar peptide sequence, is widely used, more affordable and reimbursed for use in multiple sclerosis in several countries. The Committee considered the option of listing ocrelizumab as alternative to rituximab, but also recognized the large difference in current prices of the two products which decreases ocrelizumab competitiveness. The Committee concluded that including ocrelizumab as a therapeutic alternative to rituximab could result in considerable additional expenditure at country level for patients and health systems, without offering additional clinical benefit.

Section 6: Anti-infective medicines

Section 6.2.1 Access group antibiotics

The Expert Committee recommended the inclusion of a new strength, child-friendly dispersible tablet formulation of amoxicillin + clavulanic acid (200 mg + 28.5 mg) as an Access group antibiotic on the core list of the EMLc for treatment of bacterial infections in children – specifically those infections for which amoxicillin + clavulanic acid is already recommended on the EMLc. The Committee noted that the 7:1 ratio of amoxicillin to clavulanic acid is associated with similar efficacy to the 4:1 ratio but has a reduced frequency of gastrointestinal adverse effects. The Committee endorsed the importance of age-appropriate formulations to better meet the dosing needs of children.

Section 6.2.2 Watch group antibiotics

The Expert Committee did not recommend inclusion of flomoxef sodium as a Watch group antibiotic on the EML and EMLc for empiric treatment of community acquired mild/moderate intraabdominal and upper urinary tract infections caused by extended-spectrum β-lactamase-producing Enterobacterales because of uncertainty in the available evidence.

Section 6.2.3 Reserve group antibiotics

The Expert Committee recommended the inclusion of ceftolozane + tazobactam as Reserve group antibiotic on the complementary list of the EML and EMLc for the treatment of infections caused or suspected to be caused by carbapenem-resistant *Pseudomonas aeruginosa*, a “Critical” priority pathogen on the 2017 WHO Priority Pathogens List. The Committee acknowledged that the clinical evidence for efficacy of ceftolozane + tazobactam against this specific pathogen is limited but considered that the availability of carbapenem-sparing alternatives for treatment of drug-resistant *Pseudomonas aeruginosa* was important as part of the strategy to limit/prevent further emergence and spread of carbapenem-resistant organisms.

The Committee did not recommend inclusion of imipenem + cilastatin + relebactam as a Reserve group antibiotic on the complementary list of the EML and EMLc for the treatment of infections caused by multidrug-resistant organisms. The Committee noted that imipenem + cilastatin + relebactam lacks in vitro activity against the carbapenemase genotypes most commonly associated globally with carbapenem resistance in Enterobacterales and that other antibiotics with similar spectrum of activity (e.g. cefiderocol, ceftazidime + avibactam, meropenem + vaborbactam) are already included as Reserve antibiotics on the Model Lists.

The Committee recommended inclusion of tedizolid phosphate on the complementary list of the EML as a Reserve group antibiotic for the treatment of infections caused or suspected to be caused by multidrug-resistant Gram-positive pathogens (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci), as an alternative to linezolid under a square box listing. The recommendation was based on evidence indicating that tedizolid is non-inferior to linezolid for the treatment of acute bacterial skin and skin structure infections, with a lower incidence of adverse events. However, the Committee observed that tedizolid phosphate is currently less widely available and considerably more expensive than linezolid.

Update to the AWaRe (Access, Watch, Reserve) classification of antibiotics

No changes were recommended to the classification of antibiotics as Access, Watch or Reserve. The 2023 AWaRe classification database will be updated to reflect the recommended inclusion of ceftolozane + tazobactam on the EML and EMLc and of tedizolid phosphate as a therapeutic alternative to linezolid on the EML. The AWaRe classification database is available at Web Annex C.

Section 6.2.5 Antituberculosis medicines

The Expert Committee recommended the inclusion of ethionamide on the core list of the EML and EMLc for the new indication for treatment of drug-susceptible tuberculosis meningitis in children and adolescents, as part of a 6-month intensive regimen in combination with isoniazid, rifampicin and pyrazinamide. The Committee also recommended the inclusion of pretomanid on the complementary list of the EML for treatment of multidrug-resistant or rifampicin-resistant tuberculosis, in a combination regimen with bedaquiline, linezolid with or without moxifloxacin.

The Committee recommended deletion from the EML and/or EMLc of various formulations and strengths of amikacin, ethambutol, ethionamide, isoniazid, linezolid, p-aminosalicylic acid and pyrazinamide, noting that they are not optimal formulations and strengths for tuberculosis treatment. A new strength formulation of p-aminosalicylic acid (as p-aminosalicylate sodium) was recommended for inclusion to replace the previously listed one which has been discontinued by the only manufacturer. The Committee also recommended that the age restrictions associated with the listings for bedaquiline and delamanid on the EML and EMLc should be removed.

These recommendations are fully aligned with recommendations in current WHO guidelines for tuberculosis.

Section 6.4.4.2 Medicines for hepatitis C

The Expert Committee recommended the inclusion of ravidasvir on the core list of the EML as a therapeutic alternative under the square box listing for pangenotypic direct-acting antivirals for the treatment of chronic hepatitis C virus infection in adults. Ravidasvir is pangenotypic when used in combination with sofosbuvir. The recommendation was made based on evidence of effectiveness and safety, similar to that seen with other pangenotypic direct-acting antiviral regimens.

The Committee also recommended deletion of non-pangenotypic treatment options for hepatitis C virus infection (dasabuvir, ombitasvir + paritaprevir + ritonavir, and pegylated interferon alfa 2a and 2b) from the core list of the EML. These treatments are no longer recommended in WHO guidelines for treatment of hepatitis C.

Section 6.7 (new sub-section) Medicines for Ebola virus disease

The Expert Committee recommended the addition of the monoclonal antibodies ansuvimab and atoltivimab + maftivimab + odesivimab to the core list of the EML and EMLc for the treatment of confirmed Ebola virus disease caused by Zaire ebolavirus in adults and children, and in neonates of unconfirmed infection status aged 7 days old or younger, born to mothers with confirmed infection. The Committee noted that Ebola virus disease is a life-threatening disease with a high case-fatality rate, for which effective treatments are of public health importance. The Committee considered that the available clinical trial evidence for ansuvimab and atoltivimab + maftivimab + odesivimab has demonstrated important reductions in mortality compared to standard supportive care alone. The Committee considered that their inclusion on the Model Lists would represent a strong equity and advocacy message, fully aligned with WHO guidelines, that could contribute to

broader actions being undertaken to ensure reliable, affordable access to quality-assured therapeutics for Ebola virus disease.

Section 6.8 (new sub-section) Medicines for COVID-19

Taking account of the global recognition of the need for effective therapeutics to prevent and treat COVID-19, as well as the need to ensure adequate and affordable access globally to these treatments, the Expert Committee recommended that effective and safe therapeutics for COVID-19 should be considered as essential medicines and should therefore be prioritized by countries for national selection and procurement. However, the Committee also recognized the continued rapid evolution of the evidence base for COVID-19 therapeutics, which contrasts with the 2-year update cycle of the Model Lists. Furthermore, the evolution of the SARS-CoV-2 virus, combined with changing population immunity may influence disease severity and thus have an impact on the relative and absolute benefits associated with COVID-19 therapeutics. The Committee considered that in the context of public health emergencies, there is a risk in listing medicines on the WHO Model Lists that later must be removed because they are no longer relevant for the reasons outlined above, a scenario that ideally should be avoided. The Committee recommended that countries should refer to WHO and national guidelines as tools to orient prioritization of medicines during public health emergencies.

The Expert Committee recommended a new section be added to the EML and EMLc for COVID-19 therapeutics, but that specific, individual medicines should not be listed at this time. Rather, the Committee recommended that this section of the Model Lists should direct national decision makers to the WHO living guidelines for COVID-19 therapeutics, noting that these are being revised and updated regularly. Importantly, these living guidelines also include recommendations for use of other medicines already included on the Model Lists (e.g. dexamethasone, oxygen), as well as recommendations against the use of medicines that are included on the Model Lists for other indications (e.g. hydroxychloroquine, lopinavir-ritonavir).

Section 8: Immunomodulators and antineoplastics

Section 8.1 Immunomodulators for non-malignant disease

The Expert Committee did not recommend the inclusion of sub-cutaneous injection formulations of methotrexate on the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and arthritic psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. The Committee noted that methotrexate is one of the mainstays of treatment for these conditions, but that data on clinical efficacy and safety of subcutaneous methotrexate compared to oral or intramuscular formulations are limited and are based mostly on studies in patients with rheumatoid arthritis. Overall, the Committee considered the possible benefits of subcutaneous compared to oral methotrexate were unclear, and with limited available evidence suggesting only modest benefits in a small proportion of patients, at a considerably higher price.

Section 8.2 Antineoplastic and supportive medicines

A total of 12 applications for cancer medicines were considered by the Expert Committee. These included requests for inclusion of new cancer medicines, and requests for new indications for already listed cancer medicines. Three applications (PD-1/PD-L1 immune checkpoint inhibitors for non-oncogene-addicted locally advanced and metastatic non-small cell lung cancer, osimertinib for EGFR mutated locally advanced or metastatic non-small cell lung cancer and cyclin-dependent kinase 4/6 inhibitors for hormone-receptor positive/HER2-negative advanced breast cancer) were resubmissions following recommendations not to list made by the 2021 Expert Committee. All applications were reviewed by the EML Cancer Medicines Working

Group prior to the meeting, who provided written comments to inform the Expert Committee's considerations.

Expert Committee recommendations to include new cancer and supportive medicines:

- The inclusion of pegylated liposomal doxorubicin on the complementary list of the EML and EMLc for the treatment of Kaposi sarcoma. The Committee noted evidence that pegylated liposomal doxorubicin is associated with similar or improved survival benefits and reduced harms in comparison to non-liposomal doxorubicin and other routinely used chemotherapies, and pegylated doxorubicin is a preferred therapeutic alternative to paclitaxel in children as the experience with paclitaxel in this setting is still rather limited.
- The inclusion of pegfilgrastim (including quality-assured biosimilars) on the complementary list of the EML and EMLc for primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy, and for secondary prophylaxis in patients who have experienced neutropenia following prior myelotoxic chemotherapy. The Committee noted that a single dose of pegfilgrastim (once every two weeks) is an efficacious and safe alternative to daily injections of filgrastim. The Committee considered that pegfilgrastim may offer advantages over filgrastim in settings where refrigerated storage outside of secondary treatment centers is limited. In these settings, patients being treated with filgrastim face longer hospital stays or daily clinic visits and this has been associated with lower adherence to treatment and increased risk of life-threatening infections. The Committee noted that filgrastim remains a relevant treatment option for patients in whom a treatment duration of less than 2 weeks is indicated.

Expert Committee recommendations to include new indications for existing listed cancer and supportive medicines:

- The current listings of cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, prednisolone and vinblastine on the complementary list of the EML and EMLc be extended to include the new indication of anaplastic large cell lymphoma (ALCL). These medicines are recognized as part of the standard of care for ALCL. Their benefits and harms were accepted as being well established from use in other indications in children and in adults.
- The current listings of cytarabine, immunoglobulin, mercaptopurine, methotrexate, prednisolone, vinblastine and vincristine on the complementary list of the EML and EMLc be extended to include the new indication of Langerhans cell histiocytosis (LCH). While LCH is considered a rare disease, the Committee acknowledged that treatment is associated with very high survival rates in many cases. These medicines are recognized as part of the standard of care for children with LCH. Their benefits and harms were accepted as being well established from use in other indications in children and in adults.
- The current listing for rituximab on the complementary list of the EML and EMLc be extended to include the new indication of Burkitt lymphoma. The Committee noted that rituximab, when added to standard chemotherapy, is associated with meaningful benefits in terms of event-free and overall survival in children and adolescents, with a well-known and acceptable safety profile.

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

- Cladribine for the treatment of refractory Langerhans cell histiocytosis with involvement of risk organs (a high-risk subgroup) in children and adolescents. The Committee noted that cladribine is associated with serious haematological toxicities limiting its safe use to specialist tertiary care centres and impacting the feasibility of use.
- Crizotinib for the treatment of relapsed/refractory anaplastic large cell lymphoma in children and adolescents because of insufficient evidence and toxicity concerns.
- Cyclin-dependent kinase 4/6 inhibitors (abemaciclib, palbociclib and ribociclib) for the treatment of hormone receptor positive/HER2-negative advanced breast cancer. The Committee acknowledged that clinical trial results for this class of medicines in the first- and second-line settings suggest a meaningful survival benefit when added to endocrine therapy compared with endocrine therapy alone. However, the Committee considered that uncertainties still exist regarding the optimal, most active and best tolerated dose, noting that many patients had to reduce the dose in the pivotal trials. The Committee also considered that there were uncertainties regarding the duration of treatment, positioning as first or second line in the metastatic setting, and whether clinically significant differences exist between agents within the pharmacological class. As in 2021, the Committee noted the enduring high prices of these medicines, which would pose serious affordability challenges, especially in low- and middle-income countries. The Committee recommended that data for these medicines continue to be evaluated as they evolve and reiterated the recommendation of the 2021 Expert Committee that this class of medicines be flagged to the Medicines Patent Pool as potential candidates for voluntary licensing agreements.
- Osimertinib for first-line treatment of EGFR-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The Committee acknowledged that current data show meaningful survival benefits for osimertinib, a third-generation tyrosine kinase inhibitor, compared to first- and second-generation EML-listed alternatives for this indication (erlotinib, gefitinib and afatinib). However, the Committee noted that osimertinib remains very highly priced, and as such would still be unaffordable in many low- and middle-income countries. The Committee expressed concern that the inclusion of osimertinib on the EML could worsen health inequity by diverting limited resources from less expensive alternatives (including generics) already listed on the EML for this indication. The Committee requested that data for osimertinib continue to be evaluated as they evolve and encouraged efforts to facilitate affordable access to osimertinib in low- and middle-income settings e.g., through negotiation of public health licensing agreements through the Medicines Patent Pool.
- Zanubrutinib for treatment-naïve or relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma. The Committee noted the results of clinical trials comparing zanubrutinib with bendamustine plus rituximab in previously untreated patients, and with ibrutinib in patients with relapsed/refractory disease, showed promising survival gains. However, the Committee considered that the magnitude of these gains may be limited, and that few long-term data were available. The Committee also noted important toxicity concerns (particularly neutropenia). The Committee considered that at the current high price, zanubrutinib would neither be considered cost-effective nor affordable in most low- and middle-income settings. The Committee considered that substitution of ibrutinib with zanubrutinib would not necessarily be associated with health budget savings as proposed in the application, because lower ibrutinib doses than those described in the application may be used in clinical practice.
- CD-19-directed antigen receptor (CAR) T-cells (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) for the treatment of adults with relapsed or refractory large B-cell lymphoma. The

Committee acknowledged that CAR-T cell treatment outperforms the standard of care with salvage immunochemotherapy in terms of progression free-survival, however the survival data remain immature. The Committee noted variability across trials (with one study suggesting a potential negative effect associated with CAR-T cell therapy) and limited long-term follow-up for all CAR-T therapies proposed, making the actual survival benefit uncertain. The Committee noted significant safety concerns including cytokine release syndrome and neurological toxicity that can occur in a high proportion of patients and which requires highly specialized medical management. The Committee recognized that treatment of patients using CAR-T-cell therapy requires dedicated health system resources and infrastructure well beyond those available in most settings. CAR-T cell therapy has generally been found not to be cost-effective with large budget impacts due to prohibitive production costs for administration and management of toxicities. However, the Committee noted with interest that these therapies are becoming increasingly available in academic settings and closed/semi-automated manufacturing process systems are now available which may substantially reduce prices and likely increase availability. Recognizing the promising role of CAR-T cell therapy for large B-cell lymphoma and potentially also other cancers, the Committee recommended that evidence for these therapies, as well as their growing availability and affordability should continue to be monitored by WHO.

- Programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors for the first-line treatment of non-oncogene addicted metastatic NSCLC in patients with tumour PD-L1 expression ≥ 50% (pembrolizumab, atezolizumab, cemiplimab) and of non-oncogene addicted locally advanced, unresectable NSCLC following chemo-radiotherapy in patients with tumour PD-L1 expression ≥1% (durvalumab). As was the case in 2021, the Committee accepted these medicines continue to demonstrate a relevant and meaningful survival benefit for eligible patients, and possible improvements in quality of life compared with platinum-based chemotherapy. The available evidence is particularly strong for pembrolizumab, for which overall survival benefits are maintained over 5 years. Atezolizumab and cemiplimab show similar benefits, although the available follow-up data are shorter. Similarly, durvalumab data are less mature and will require further consideration. The Committee considered that an overall net benefit can be reasonably assumed for the entire class when compared to platinum-based chemotherapies. However, more data are needed regarding the optimal doses and duration of treatment, with some data already suggesting that for several immune checkpoint inhibitors, lower doses and shorter durations may be sufficient. In principle, the Committee considered that the availability of several immune checkpoint inhibitors as therapeutic options can boost competition and facilitate affordable access. These considerations notwithstanding, the Committee noted that prices for immune checkpoint inhibitors remain prohibitively high in most settings, and global access to affordable companion diagnostic tests is limited. Coupled with the high global prevalence of non-small cell lung cancer, the opportunity costs of providing treatment with immune checkpoint inhibitors would be substantial for many health systems and would divert limited available resources from other public health programmes. The Expert Committee encouraged WHO to continue to work on strategies to address the issue of high prices of effective cancer medicines and identify solutions to facilitate increased affordable access.
- Tislelizumab for the treatment of non-oncogene addicted locally advanced and metastatic NSCLC, without patient preselection based on PD-L1 tumour expression. The Committee noted that survival data from clinical trials comparing tislelizumab plus chemotherapy versus chemotherapy alone were immature, with less than two years of follow-up, and therefore, while promising based on the available data, the overall survival benefit was still uncertain. The Committee acknowledged that the

reported price of tislelizumab in China (the only country where tislelizumab is currently approved and available for this indication) was notably lower than the price of other immune checkpoint inhibitors in this setting.

- Toripalimab for the treatment of locally advanced or metastatic nasopharyngeal and oesophageal cancers. The Committee noted that the survival benefit observed when toripalimab is added to chemotherapy for first-line treatment of advanced nasopharyngeal cancer was currently modest, and that toripalimab had been assigned a score of 3 on the ESMO Magnitude of Clinical Benefit Scale (below the accepted score for cancer medicines on the EML). For advanced oesophageal cancer, the Committee noted that toripalimab plus chemotherapy compared to chemotherapy alone might meaningfully improve survival, however the available evidence was still preliminary with only a short follow-up. The Committee acknowledged that the reported price of toripalimab in China (the only country where toripalimab is currently approved and available for these indications) was considerably lower than other immune checkpoint inhibitors in this setting.

Section 9: (re-named) Therapeutic foods

The Expert Committee recommended the inclusion of ready-to-use therapeutic food (RUTF) on the core list of the EMLc for the treatment of severe acute malnutrition in children aged 6 months to 5 years based on evidence from systematic reviews that demonstrated that the use of RUTF is associated with important benefits in terms of nutritional recovery and weight gain compared to standard care. The Committee was satisfied with the information provided by the applicants addressing the specific concerns highlighted by the 2019 Expert Committee regarding potential consequences of including RUTF on the Model List and associated risk-mitigation measures. The Committee was also reassured by the publication of Codex Alimentarius guidelines which define the nutritional composition, production and labelling standards for RUTF as a food for special medical purposes.

Section 10: Medicines affecting the blood

Section 10.1 Antianaemia medicines

The Expert Committee recommended the inclusion of a new strength formulation of ferrous salt + folic acid (60 mg elemental iron + 2.8 mg folic acid) on the core list of the EML as a weekly-administered supplement for prevention of anaemia in menstruating women and adolescent girls, and for reducing the risk of neural tube defect-affected pregnancies. The Committee noted that weekly intermittent supplementation with this formulation was associated with similar outcomes as daily iron and folic acid supplementation and is likely to be associated with advantages in terms of adherence. The Committee also noted that weekly iron and folic acid supplementation is recommended in multiple WHO guidelines.

Section 10.3 Other medicines for haemoglobinopathies

The Expert Committee recommended that oral deferasirox be transferred to the core list of the EML and EMLc for use in the treatment of transfusional iron overload in patients with thalassaemia syndromes, sickle cell disease and other chronic anaemias, with a square box listing specifying oral deferiprone as a therapeutic alternative. The Committee also recommended that intravenous deferoxamine should remain listed on the complementary list of the EML and EMLc for these indications, and the square box associated with the current listing be removed. The Committee accepted that the comparative efficacy and safety of deferiprone, deferoxamine and deferasirox were generally similar, and that orally administered treatments may be preferred options. The Committee recognized the value in having multiple iron chelating agents included on the Model Lists to enable countries to make appropriate national selection decisions taking into consideration relevant contextual factors.

Section 11: Blood products of human origin and plasma substitutes

Section 11.1 Blood and blood components

The Expert Committee recommended the inclusion of pathogen-reduced cryoprecipitate on the core list of the EML and EMLc with a square box to indicate non-pathogen-reduced cryoprecipitate as a therapeutic alternative. The Committee noted that cryoprecipitate is used to replace coagulation factors in cases of massive haemorrhage, von Willebrand disease, and deficiency of coagulation factor XIII. It may also be used as an alternative to coagulation factor VIII concentrate in haemophilia A in settings where this is unavailable or unaffordable. The Committee also noted that pathogen reduction of cryoprecipitate can reduce the risk of transmission of blood-borne infectious agents and has been associated with lower risks of alloimmunization and allergic transfusion reactions compared to other blood components.

Section 11.2.2 Blood coagulation factors

The Expert Committee did not recommend inclusion of recombinant coagulation factors or bypassing agents as therapeutic alternatives to plasma-derived coagulation factors under the square box listings for coagulation factors VIII and/or IX on the EML and EMLc. The Committee advised that future consideration for the inclusion of these products on the Model Lists will require full applications, compliant with the requirements for EML applications and containing all relevant information, so that the available evidence can be evaluated in line with standard procedures.

The Committee recommended that the square box be removed from the current listing of coagulation factor VIII, noting that other proposed alternatives (desmopressin and cryoprecipitate) are included in the Model Lists as independent listings. The Committee recommended the inclusion of additional strength formulations (250 IU and 1000 IU per vial) of factor VIII, acknowledging that these are the most commonly used and available formulations.

The Committee agreed that coagulation factor IX complex is a suitable therapeutic alternative to coagulation factor IX in situations where purified factor IX is not available. The Committee therefore recommended that coagulation factor IX complex be included as a therapeutic alternative under the current square box listing for factor IX.

The Committee did not recommend removal of dextran from the Model Lists. While it is not used in the treatment of haemophilia, it remains an essential plasma substitute for patients in need of blood volume replacement.

Section 12: Cardiovascular medicines

Section 12.5.1 Anti-platelet medicines

The Expert Committee did not recommend the addition of ticagrelor to the core list of the EML for the prevention of atherothrombotic events in adults with acute coronary syndromes or high-risk patients with a history of myocardial infarction. The Committee considered that there was uncertainty in efficacy outcomes across trials comparing ticagrelor and clopidogrel and among different patient sub-populations. The Committee also noted that ticagrelor was associated with significantly increased risks of some important bleeding outcomes (e.g., fatal intracranial bleeding). Further, while it was noted that while generics of ticagrelor are available, it remains more expensive than clopidogrel in many settings.

Section 12.7 (new sub-section) Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease

The Committee recommended the inclusion of three fixed-dose combinations of cardiovascular medicines (acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide; acetylsalicylic acid + atorvastatin

+ ramipril; atorvastatin + perindopril + amlodipine) on the core list of the EML for use in primary and secondary prevention of atherosclerotic cardiovascular diseases. Components of the combinations are listed with a square box, indicating other medicines within the respective pharmacological classes represent therapeutic alternatives, consistent with the current square box listings for hydrochlorothiazide, antihypertensives and statins. The Committee noted evidence from large randomized-controlled trials that indicate that use of these combinations is associated with reduced risks of cardiovascular events, including fatal and non-fatal myocardial infarction and stroke and the need for revascularization in primary and secondary prevention settings. The Committee also noted data that indicates that the combination products are associated with improved adherence and quality of life, at prices equal to or lower than multiple component monotherapies. This recommendation notwithstanding, the Committee emphasized that the ongoing availability of single agent cardiovascular medicines was critical to allow treatment modification where necessary, and that combination products should not displace single components at country level. The Committee further considered that guidance concerning the most appropriate use of these FDCs for different indications should be provided in separate WHO guidance documents.

Section 13: Dermatological medicines

The Expert Committee did not recommend the inclusion of sunscreen on the EML and EMLc for the prevention of skin cancer in people with albinism or xeroderma pigmentosum. The Committee acknowledged the public health relevance and effectiveness of sunscreen in preventing skin cancer especially in high-risk subgroups such people with albinism or xeroderma pigmentosum, but also in the general population. The Committee agreed that the use of sunscreens, as well as other sun-protection and sun-avoidance strategies and behaviors are important, effective preventive interventions to reduce the incidence and prevalence of skin cancers, including melanoma. The Committee also noted that the global burden of disease of such cancers is increasing, and that their treatment is associated with considerable costs for both individuals and health systems.

The Committee considered that before being able to recommend sunscreen products for inclusion on the Model Lists, it would be necessary to define relevant standards and specifications for therapeutic (as distinct from cosmetic) sunscreen products protecting against both UVA and UVB rays (i.e. broad spectrum). This would include details of specific active ingredients and their concentration, and the range of sun protection factor rating. This information needs to be supported by evidence and implications for labelling standards, to provide clear and reliable guidance for countries for selection of the most appropriate sunscreen products.

Section 13.4 Medicines affecting skin differentiation and proliferation

The Expert Committee acknowledged the global burden of psoriasis and the public health need for effective treatments. Until now, only topical therapies for psoriasis have been included on the Model Lists. The Committee recommended the inclusion of methotrexate on the complementary list of the EML and EMLc for the new indication of psoriasis, based on a favourable balance of desirable to undesirable effects. The Committee did not recommend the inclusion of ustekinumab on the EML for the treatment of severe psoriasis in adults. The Committee recognized the important role of biological disease-modifying agents in the management of moderate to severe psoriasis. The Committee requested that a comprehensive review of all biological disease-modifying medicines in the treatment of moderate to severe forms of psoriasis be undertaken to inform future consideration for EML and EMLc listing.

Section 18: Medicines for endocrine disorders

The Expert Committee did not recommend inclusion of the vitamin D analogues alfacalcidol and calcitriol on the complementary list of the EML and EMLc, for the proposed indications of hypoparathyroidism,

hypophosphataemic rickets, hypocalcaemic vitamin D dependent/resistant rickets, neonatal hypocalcaemia, chronic kidney disease, and other disorders of vitamin D metabolism or transport. While the application included reference to conditional guideline recommendations for the use of vitamin D analogues in chronic kidney disease, hypophosphataemic rickets and hypoparathyroidism, overall, the Committee noted that evidence base was uncertain due to risk of bias, indirectness when assessing patient-important outcomes, inconsistencies, and imprecision. The Committee considered that the limited likelihood of influencing important clinical outcomes was potentially outweighed by the risks associated with the use of alfacalcidol and calcitriol, such as hypercalciuria, decrease in renal function and cardiovascular risk.

The Expert Committee did not recommend the inclusion of phosphorus on the complementary list of the EMLc, for the treatment of hypophosphataemic rickets in children. The Committee noted evidence from small cohort studies which suggests that early introduction of treatment with phosphorus and vitamin D in children with hypophosphataemic rickets has beneficial effects in terms of growth, improved bone mineralization and reduced bone deformities. However, the Committee considered that hypophosphataemic rickets is a relatively rare condition which constitutes only a small sub-group of all hypophosphataemic conditions that may benefit from phosphorus supplementation. The Committee therefore considered that a comprehensive review of the evidence for phosphorus treatment across all conditions for which it is indicated should be requested for future consideration.

The Expert Committee did not recommend inclusion of zoledronic acid on the EML and EMLc for the new indication of osteogenesis imperfecta. The Committee noted that available evidence suggests that bisphosphonates may increase bone mineral density but considered that the benefits of bisphosphonate treatment on other important outcomes such as fracture risk, bone pain and physical functioning were unclear.

The Expert Committee did not recommend inclusion of ketoconazole on the EML for the treatment of Cushing syndrome. The Committee noted that the available evidence suggests that a significant proportion of patients have a good response to treatment with ketoconazole, however, the certainty of evidence was low, and there are serious concerns about the safety profile associated with systemic use of ketoconazole, including potentially severe liver toxicity, and the potential for numerous drug-drug interactions.

The Expert Committee did not recommend inclusion of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to the core list of the EML for weight loss in obesity because of uncertain long-term clinical benefit and safety in this patient population. The Committee noted that GLP-1 RAs have been shown to reduce weight and body mass index in the short-term compared to placebo. However, data are lacking on long-term effectiveness, optimal duration of treatment, maintenance of weight reduction once the therapy is stopped, and effect on other clinically important outcomes (e.g. hypertension or hyperglycaemia). Long-term safety data are also lacking.

Section 18.3 Estrogens

The Expert Committee did not recommend inclusion of 17-ß-estradiol on the complementary list of the EML for the management of pubertal development in adolescents with primary or secondary ovarian failure. The Committee considered that the application reported insufficient information on the evidence supporting the use of estradiol for the proposed indication, including optimal dosages and formulations. The Committee noted that global prevalence of primary ovarian failure or primary ovarian insufficiency varies among different populations but is generally low. The Committee considered that re-evaluation of estradiol should be made

considering additional indications for which estradiol is routinely used, such as hormone replacement therapy in menopause or following hysterectomy.

Section 18.5.1 Insulins

The Expert Committee recommended that the current listings for human insulin on the core list of the EML and EMLc be extended to include cartridge and pre-filled pen delivery systems. The Committee considered that cartridges and pre-filled pens may offer advantages for patients over vials and syringes in terms of ease of use, greater accuracy of dosing and improved adherence. The Committee acknowledged that affordable access to insulin products remains a critical global health priority.

Section 18.6 Medicines for hypoglycaemia

The Expert Committee did not recommend the inclusion of somatropin on the complementary list of the EMLc for the management of hypoglycaemia secondary to growth hormone deficiency in neonates, infants and young children. The Committee acknowledged that the management of hypoglycaemia, of any etiology, in neonates and infants is critical to prevent permanent neurological sequelae. However, the Committee considered that comparative evidence for somatropin versus other medicines for management of hypoglycaemia currently included on the Model Lists (e.g. diazoxide, glucagon, glucose) and information regarding the comparative costs and cost-effectiveness would be necessary to inform any future consideration for somatropin in this indication.

Section 18.8 (new sub-section) Medicines for disorders of the pituitary hormone system

The Expert Committee recommended the inclusion of cabergoline on the core list of the EML for the medical management of hyperprolactinaemia associated with prolactin-secreting pituitary adenomas (prolactinomas). Listing was recommended with bromocriptine as a therapeutic alternative under a square box listing. Overall, the Committee considered that the available evidence suggests medical therapy with dopamine agonists can achieve prolactin normalization in most patients. The Committee noted that dopamine agonist therapy is a preferred first-line intervention for management of hyperprolactinaemia and prolactinomas and may be the only option in settings where specialist neurosurgery is not available, or in patients for whom surgery is not feasible. Listing was recommended with bromocriptine as therapeutic alternative under a square box listing. Cabergoline may be superior to bromocriptine in decreasing the serum prolactin concentration and has fewer adverse effects but is usually more costly.

The Expert Committee recommended the inclusion of octreotide immediate-release and modified-release injections on the complementary list of the EML for use in the management of gigantism and acromegaly in adults with growth hormone-producing tumours. The Committee noted that transsphenoidal surgery is the treatment of first choice for this condition but accepted that pharmacological treatment with somatostatin analogues is an effective alternative in situations where surgery is not possible or available. The Committee did not recommend the inclusion of lanreotide depot injection either as an individual listing or as a therapeutic alternative to octreotide, because it was not shown to be superior to octreotide, is more expensive, and unlike octreotide, is not yet available as generics.

Section 19: Immunologicals

Section 19.3 Vaccines

This section was reviewed by the Secretariat for consistency and full alignment with the latest WHO recommendations for routine immunization (March 2023). No changes to the current vaccine listings on the EML and EMLc were required.

Section 21: Ophthalmological preparations

The Expert Committee did not recommend inclusion of hypromellose on the EML and EMLc for the treatment of dry eye disease in adults and children. The Committee accepted that hypromellose is a safe and effective ocular surface lubricant for reducing the signs and symptoms of dry eyes, especially for patients with mild to moderate symptoms. However, the Committee considered that the sight-threatening complications of dry eye disease are primarily associated with severe forms of the condition. There was limited evidence comparing hypromellose versus other artificial tear preparations, including combinations, for improvement in relevant clinical outcomes, specifically in patients with severe dry eye disease.

Section 22: Medicines for reproductive health and perinatal care

Section 22.2 Ovulation inducers

The Expert Committee recommended inclusion of letrozole on the complementary list of the EML for the treatment of anovulatory infertility associated with polycystic ovary syndrome or unexplained infertility. Listing was recommended with anastrozole as a therapeutic alternative under a square box listing. The Committee noted evidence that letrozole is associated with a moderate increase in live births and clinical pregnancies compared to clomifene (a medicine currently included in the EML) in patients with infertility due to polycystic ovary syndrome, and similar efficacy to clomifene for live births or biochemically tested pregnancy in couples with unexplained infertility. The Committee noted that WHO guidelines for the prevention, diagnosis and treatment of infertility are in development, and are expected to include recommendations for use of letrozole for ovulation induction in these populations.

Section 22.3 Uterotonics

The Committee recommended that the current listing of mifepristone + misoprostol on the core list of the EML be extended to include the new indication of medical management of intra-uterine fetal demise. The Committee noted evidence that the combination regimen was associated with higher rates of expulsion and shorter expulsion times than misoprostol alone. The Committee considered that adverse effects associated with use of the combination were generally mild, well-known and manageable. The Committee also noted that the medical management of intra-uterine fetal demise using this combination regimen has been included in WHO guidelines for medical management of abortion since 2018.

Section 24: Medicines for mental and behavioural disorders

A total of 16 applications for medicines for mental health conditions and substance use disorders were considered by the Expert Committee. Many were developed by, or in consultation with the WHO Department of Mental Health and Substance Use with the goal of optimizing alignment between the Model Lists and recommendations in relevant WHO guidelines.

Section 24.1 Medicines used in psychotic disorders

The Expert Committee recommended the removal of chlorpromazine immediate-release injection from the core list of the EML for the treatment of schizophrenia and related psychoses because of a lack of high-quality evidence of benefit versus either placebo, or the alternative EML-listed haloperidol immediate-release injection, with a likely increased risk of adverse effects. The Committee recommended inclusion of olanzapine immediate-release injection on the core list of the EML for the acute treatment of schizophrenia and related psychoses based on evidence of similar effectiveness and greater tolerability compared to haloperidol immediate-release injection.

The Expert Committee did not recommend inclusion of paliperidone palmitate 3-month long-acting injection on the EML for maintenance treatment of schizophrenia. The Committee noted that compared to the 1-month

formulation, the 3-month formulation has evidence of similar clinical efficacy and safety and may offer advantages to patients in terms of fewer injections. However, the Committee noted that it is not recommended to initiate treatment with the 3-month formulation, rather it is used in patients who demonstrate benefit and tolerance to the 1-month formulation over at least 4 months. In addition, the 3-month formulation is more highly priced, not yet available as generic, and currently has limited availability in low- and middle-income countries.

The Expert Committee recommended the addition of a square box to the listing of risperidone on the EML for treatment of schizophrenia and related chronic psychotic disorders, specifying oral aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives. The Committee noted that evidence from several high-quality meta-analyses on the acute and maintenance treatment of schizophrenia and other chronic psychoses that found most oral second-generation antipsychotics were similarly effective and tolerable.

The Expert Committee recalled the request made by the 2021 Committee that therapeutic alternatives for the square box listings for chlorpromazine, fluphenazine and haloperidol in this section of the EML be reviewed. The Expert Committee accepted the rationale applied by the WHO Department of Mental Health and Substance Use in identifying suitable therapeutic alternatives, and made the following recommendations:

- Chlorpromazine (oral formulations only) be included as a therapeutic alternative to oral haloperidol. (This recommendation, coupled with the recommendation above to remove chlorpromazine injection, effectively removes the independent listing for chlorpromazine from the EML).
- Haloperidol decanoate and zuclopenthixol decanoate be included as therapeutic alternatives to fluphenazine (decanoate/enantate).

The Expert Committee recommended the deletion of chlorpromazine and haloperidol (all dosage forms) from the complementary list of the EMLc. The Committee noted that schizophrenia and other chronic psychotic disorders are rare in children younger than 12 years. The Committee agreed that the available evidence for these medicines in the treatment of psychoses in children was inconclusive and insufficient to support their ongoing inclusion on the EMLc.

Section 24.2.1 Medicines used in depressive disorders

The Expert Committee recommended that square box should be removed from the current listing for amitriptyline for the treatment of depressive disorders on the EML. The Committee considered that there are insufficient data to support the inclusion of other tricyclic antidepressants as therapeutic alternatives for amitriptyline. The Committee considered that amitriptyline is the tricyclic antidepressant with the larger evidence base and other molecules have insufficient evidence, or are likely to be inferior to amitriptyline in some relevant dimension (e.g., clomipramine is likely to be less acceptable to patients than amitriptyline and placebo).

The Expert Committee recommended the deletion of fluoxetine for the treatment of depressive disorders in children from the complementary list of the EMLc. The Committee accepted that fluoxetine may be used in children younger than 12 years in some setting where there is limited access to mental health facilities and non-pharmacological interventions and may be recommended in some consensus guidelines. However, the Committee noted that the reported prevalence of depression in children younger than 12 years is low and considered that the current evidence for use of fluoxetine in this age group was inconclusive and insufficient to support its ongoing inclusion the EMLc. This recommendation therefore also applies to the listing of fluoxetine on the EMLc in Section 2.3 Medicines for other common symptoms in palliative care. The Committee noted that the prevalence of depression substantially increases throughout adolescence and into

adulthood and confirmed that fluoxetine will remain included on the EML for the treatment of depression in adults.

The Expert Committee did not recommend the inclusion of phenelzine on the complementary list of the EML for use in treatment-resistant depression because of uncertain evidence for benefit in the proposed patient population, and increased risk of harms. The Committee noted that the systematic reviews and meta-analyses presented in the application which evaluated the comparative efficacy of phenelzine versus placebo or other antidepressants did not include participants with treatment-resistant depression. The Committee also noted that phenelzine is associated with potentially serious adverse effects and has high potential for drug-drug and drug-food interactions. Treatment with phenelzine therefore would require careful and specialized monitoring and management, which may not be available in many low- and middle-income settings.

Section 24.2.2 Medicines used in bipolar disorders

The Expert Committee recommended the inclusion of quetiapine, with a square box indicating aripiprazole, olanzapine and paliperidone as specified therapeutic alternatives, on the core list of the EML for treatment of bipolar disorders. The Committee considered that the evidence presented in the application demonstrated the effectiveness of the proposed second-generation antipsychotics in the acute treatment and long-term prevention of mania/hypomania and/or depression in bipolar disorders was similar to that of classic mood stabilizers currently included on the EML (carbamazepine, lithium carbonate and valproic acid). All proposed medicines were shown to be either superior or non-inferior to placebo for acceptability (determined by all-cause discontinuations). The Committee agreed that second-generation antipsychotics have an important role in bipolar disorders in patients who do not adequately respond to or experience adverse events from mood stabilizers. Moreover, the Committee noted that the two classes of medicines may be used in combination in selected patients in clinical practice.

Section 24.3 Medicines for anxiety disorders

The Expert Committee recommended the addition of a note to the listing of diazepam in this section of the EML to indicate use is only recommended for the short-term emergency management of acute and severe anxiety symptoms as the balance of benefits and risks of diazepam use under these circumstances is considered favourable. The Committee also recommended that lorazepam should be specified as the only therapeutic alternative under the square box listing for diazepam for this indication. These recommendations are aligned with expected recommendations in updated mhGAP guidelines.

The Expert Committee recommended the inclusion of fluoxetine on the EML for the new indications of use in generalized anxiety disorder, panic disorder, and social anxiety disorder. Listing is recommended with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline as therapeutic alternatives. The Committee considered that the evidence presented in the application supported the use of fluoxetine and the proposed alternative selective serotonin reuptake inhibitors (SSRIs) for these indications as they were shown to be more effective than placebo in reducing anxiety symptoms and have a well-known and acceptable safety profile.

Section 24.4 Medicines used for obsessive compulsive disorders

The Expert Committee recommended the inclusion of fluoxetine on the EML for the new indication of obsessive-compulsive disorder in adults. Listing is recommended with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline as therapeutic alternatives. The Committee considered that the evidence presented in the application supported the use of fluoxetine and the proposed alternative

SSRIs for the treatment of obsessive-compulsive disorder, indicating that SSRIs are more effective than placebo in reducing obsessive-compulsive symptoms, and have a more favourable safety profile than tricyclic antidepressants.

Section 24.5 Medicines for disorders due to psychoactive substance use

This section of the Model Lists has been updated to include separate sub-sections for medicines for alcohol, nicotine and opioid use disorders.

Section 24.5.1 (new sub-section) Medicines for alcohol use disorders

The Expert Committee recommended the inclusion of acamprosate and naltrexone on the core list of the EML for the treatment of alcohol use disorder in adults. The Committee considered that the available evidence showed these medicines to be associated with moderate improvements in abstinence rates, which would translate to meaningful impact at the population level. Both medicines are generally well tolerated and are recommended in WHO guidelines. The Committee considered that the availability of different medicines for alcohol use disorder would provide valuable options and choice for patients and clinicians, and could facilitate increased market competition, reduce costs and improve affordable access for national health systems.

Section 24.5.2 (new sub-section) Medicines for nicotine use disorders

The Expert Committee recommended the inclusion of nicotine lozenges and mouth spray on the core list of the EML as additional forms of nicotine replacement therapy for tobacco and smoking cessation. The Committee noted high-quality evidence from multiple randomized controlled trials that all licensed forms of nicotine replacement therapy are effective at increasing increase cessation rates. The Committee considered that the availability of different forms of nicotine replacement therapy would provide options and choice for patients and clinicians, and could facilitate increased market competition, reduce costs and improve affordable access for national health systems.

Section 29: Medicines for diseases of joints

Section 29.3 Juvenile joint diseases

The Expert Committee recommended the inclusion of triamcinolone hexacetonide on the complementary list of the EML and EMLc for use in the treatment of juvenile idiopathic arthritis. Listing is recommended with a square box to indicate triamcinolone acetonide as a therapeutic alternative for national selection in situations where triamcinolone hexacetonide is not available. The Committee noted that the evidence indicates that triamcinolone hexacetonide is superior to triamcinolone acetate in terms of efficacy and duration of response but has been subject to availability and supply shortages worldwide. As was the case in 2021, the Committee considered that the available evidence was still limited, and of sub-optimal quality, but accepted that use of intra-articular glucocorticoid injections with triamcinolone (hexacetonide, and to a lesser extent acetonide) may be associated with improvements in joint inflammation in oligoarticular forms of juvenile idiopathic arthritis and have advantages over long-term systemic corticosteroid use in terms of harms.

The Expert Committee did not recommend the inclusion of anakinra for treatment of systemic onset juvenile idiopathic arthritis (SOJIA) with macrophage activation syndrome (MAS), nor of tocilizumab for treatment of SOJIA on the EML and EMLc. As was the case when these medicines were considered in 2021, the Expert Committee considered that the clinical benefits and safety of these medicines (including risk of infection) remain uncertain based on the limited available evidence. The Committee also considered that the feasibility of use of these medicines, particularly in low-resource settings was unlikely given their current high prices, and requirements for specialized care and monitoring and management of adverse events.

Section 30: (re-named) Dental medicines and preparations

The Expert Committee recalled the request made by the 2021 Committee for WHO to identify the alternative fluoride-containing formulations recommended for use in the prevention of dental caries in order that they be clearly defined in the Model Lists to provide clear guidance to countries. The Committee considered that the evidence presented in the applications for fluoride gel, mouthrinse and varnish supported the effectiveness and safety of these products in the prevention of dental caries, and therefore recommended their inclusion on the core list of the EML and EMLc, as specific fluoride-containing formulations.

The Committee also recommended the inclusion of resin-based composites on the core list of the EML and EMLc for use as dental sealants (low-viscosity forms) and as filling materials (high-viscosity forms) in the prevention and treatment of dental caries. The Committee noted that these products are effective and safe and have functional and aesthetic advantages compared to glass ionomer cement, however they require more specialized expertise and facilities for application. The Committee noted that the availability of effective alternatives to dental amalgam is important to enable parties to the Minamata Convention on Mercury to achieve the mandated phase-down of dental amalgam use, decreasing environmental mercury pollution.

Other matters considered by the Expert Committee

Age-appropriateness of formulations of essential medicines for children

In consideration of the review of the age-appropriateness of formulations of medicines on the EMLc, and the comparison report of the EML versus EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the application. The Committee also endorsed the proposals for further review of the public health relevance and evidence of specific medicines for use in children for potential future consideration for inclusion on the EMLc. The Committee noted and welcomed the ongoing review being coordinated by the Secretariat for the remaining sections of the EMLc for consideration by the 2025 Expert Committee.

Off-label use of medicines

The Expert Committee noted the comments received from the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) regarding off-label use of medicines included on the Model Lists. The Committee reiterated the views expressed by the 2015 Expert Committee regarding consideration of medicines for inclusion on the Model Lists for off-label uses or indications. Namely, that labelling is the responsibility of national regulatory authorities, and there may consequently be different labels for the same product in different countries, and that there is thus no global standard for what is considered “off-label”. Furthermore, updating approved labels for older products may not be pursued by market authorization holder(s) if doing so it is not determined to be commercially viable, and that there are many examples of older products whose regulatory labels are inconsistent with current clinical evidence and current clinical practice. Consequently, the Expert Committee reaffirmed that off-label status of a medicine need not be a reason to exclude it from the Model Lists if it otherwise meets the criteria for inclusion. Because of the intended global audience of the Model Lists and the differences in national regulatory labeling, the Committee recommended that off-label status should not be specifically marked in the Model Lists. The Committee recognized that it is a responsibility of relevant national decision-makers to consider national labeling and legal requirements in the selection and use of medicines at the country level. The Committee considered that the inclusion on the Model Lists of those off-label medicines that are associated with relevant clinical benefits and financial advantages can play an important role in informing national selection and facilitating progress towards universal health coverage.

Rare diseases

Medicines to treat rare diseases have been included on the Model Lists since the first EML was published in 1977. The Expert Committee acknowledged that rare diseases comprise a diverse group of conditions that individually, affect a small portion of the population. However, collectively, they can affect millions of people worldwide. There is no universally agreed definition of ‘rare’, with prevalence-based national and regional definitions of rare diseases (often in the context of orphan medicine legislation) varying considerably. Furthermore, a disease may be considered rare in one population or setting, while being highly prevalent in another, as disease prevalence can vary depending on various population-specific, environmental and geographic factors. The Committee also noted that with increasing advancements in precision medicine and targeted treatments in some areas (e.g., oncology), small/rare sub-categories of otherwise more common diseases are emerging. The Committee noted that many, but not all medicines for rare diseases are highly priced and may be unaffordable for many patients and healthcare systems, particularly in low-resource settings.

The Expert Committee recognized the role of the Model Lists in providing an evidence-based blueprint to inform decision-making for national essential medicines lists, including selection of medicines for rare diseases. The Committee also recognized the important advocacy role that inclusion on the Model Lists can play in fostering further actions that can lead to increased access and affordability of essential medicines for rare diseases. The Committee considered that the low prevalence of a disease need not be a reason to exclude medicines for its treatment from the Model Lists if they otherwise meet the criteria for inclusion.

Procedures for updating the WHO Model Lists

The Expert Committee noted that the procedure for updating the Model Lists has only been updated once since the publication of the first EML in 1977. The Committee also took note of the fact that since the revised procedures were introduced in 2001 (as outlined in Executive Board document EB109/8) the medicine evaluation landscape has become increasingly complex and that some aspects of the procedure may benefit from revision. Issues that were discussed by the Committee and can be considered as part of a broader discussion with Member States are: the actual application process, including how to balance the quality of the applications against the openness of the process that accepts applications without filtering them for quality, the issues surrounding effective but highly priced medicines which pose difficulties as feasibility and acceptability could be low, the role of products commonly not classified as medicines on the list such as condoms, oxygen and toothpastes, the role of the Model Lists in those clinical areas where WHO does not have guidelines, the dissemination of the Model Lists and the role with national lists to facilitate progress towards universal health coverage, and the role of the Model Lists in the context of public health emergencies of international concern. The Committee therefore recommended WHO to consider initiating a process to reassess the procedure for updating WHO's Model Lists of Essential Medicines. This should be an inclusive collaboration with Member States and other relevant stakeholders, including for example other UN organizations, WHO Collaborating Centres, universities and scientific societies, international procurement agencies, non-governmental organizations, professional associations, national essential medicines programme representatives, representatives from the pharmaceutical industry, and patients' organizations.

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/24th-eml-expert-committee

Table 1: Recommended changes on the 2023 EML

EML – New medicines added	
Medicine	**Indication**
Acamprosate	Alcohol use disorder
Acetylsalicylic acid + atorvastatin + ramipril	Prevention of atherosclerotic cardiovascular diseases
Acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide	Prevention of atherosclerotic cardiovascular diseases
Ansuvimab	Ebola virus disease
Atoltivimab + maftivimab + odesivimab	Ebola virus disease
Atorvastatin + perindopril + amlodipine	Prevention of atherosclerotic cardiovascular diseases
Cabergoline	Hyperprolactinaemia
Ceftolozane + tazobactam	Multidrug resistant bacterial infections
Cladribine	Multiple sclerosis
Cryoprecipitate, pathogen-reduced	Bleeding disorders
Deferasirox	Iron overload
Glatiramer acetate	Multiple sclerosis
Letrozole	Infertility
Levetiracetam	Partial- and generalized-onset seizures, status epilepticus
Naltrexone	Alcohol use disorder
Octreotide	Gigantism and acromegaly
Olanzapine	Schizophrenia and related psychoses
Pegfilgrastim	Febrile neutropenia prophylaxis
Pegylated liposomal doxorubicin	Kaposi sarcoma
Pretomanid	Multidrug-resistant tuberculosis
Quetiapine	Bipolar disorder
Resin-based composites	Dental caries
Ravidasvir	Hepatitis C virus infection
Sevoflurane	General anaesthesia
Triamcinolone hexacetonide	Juvenile idiopathic arthritis
EML - New indications	
Medicine	**Indication**
Cyclophosphamide	Anaplastic large cell lymphoma
Cytarabine	Anaplastic large cell lymphoma, Langerhans cell histiocytosis
Dexamethasone	Anaplastic large cell lymphoma
Doxorubicin	Anaplastic large cell lymphoma
Ethionamide	Drug-susceptible tuberculosis meningitis
Etoposide	Anaplastic large cell lymphoma
Fluoxetine	Generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive-compulsive disorder
Ifosfamide	Anaplastic large cell lymphoma
Immunoglobulin	Langerhans cell histiocytosis
Mercaptopurine	Langerhans cell histiocytosis
Methotrexate	Anaplastic large cell lymphoma, Langerhans cell histiocytosis, psoriasis
Mifepristone – misoprostol	Intrauterine fetal demise

Prednisolone	Anaplastic large cell lymphoma, Langerhans cell histiocytosis
Rituximab	Multiple sclerosis, Burkitt lymphoma
Vinblastine	Anaplastic large cell lymphoma, Langerhans cell histiocytosis
Vincristine	Langerhans cell histiocytosis
EML - New formulation/strength	
Medicine	**Formulation/strength**
Arsenic trioxide	Concentrate for solution for infusion: 2 mg/mL
Calcium folinate	Injection: 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule
Carbamazepine	Tablet (scored): 400 mg
Cefotaxime	Powder for injection: 500 mg; 1 g; 2 g (as sodium) in vial
Ceftriaxone	Powder for injection: 500 mg (as sodium) in vial
Cytarabine	Injection: 100 mg/mL
Dacarbazine	Powder for injection: 200 mg in vial
Daunorubicin	Injection: 2 mg /mL; 5 mg/mL in vial Powder for injection: 20 mg in vial
Doxorubicin	Injection: 2 mg/mL (hydrochloride) in 5 mL, 25 mL vial
Enalapril	Tablet: 10 mg (as hydrogen maleate)
Etoposide	Powder for injection: 100 mg (as phosphate) in vial
Ferrous salt + folic acid	Tablet: equivalent to 60 mg elemental iron + 2.8 mg folic acid
Fluoride	Gel: containing 2500 to 12 500 ppm fluoride (any type) Mouthrinse: containing 230 to 900 ppm fluoride (any type) Varnish: containing 22 500 ppm fluoride (any type)
Furosemide	Injection: 10 mg/mL in 5 mL ampoule Tablet: 20 mg
Insulin injection (soluble)	Injection: 100 IU/mL in 3 mL cartridge or pre-filled pen.
Intermediate-acting insulin	Injection: 100 IU/mL in 3 mL cartridge or pre-filled pen.
Methotrexate	Injection: 50 mg/2 mL (Section 8.2.1) Concentrated injection: 1000 mg/10 mL (Section 8.2.1)
Nicotine replacement therapy	Lozenge: 2 mg, 4 mg Oral spray: 1 mg per actuation
p-aminosalicylate sodium	Powder for oral solution: 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid)
Pegaspargase	Powder for injection: 3,750 units in vial
Pentamidine	Powder for injection: 300 mg (as isethionate) in vial
Valproic acid (sodium valproate)	Injection: 100 mg/mL in 3 mL ampoule
EML – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Amikacin	Injection: 100 mg/2 mL (as sulfate) in 2 mL vial (Section 6.2.5)
Chloramphenicol	Capsule 250 mg Oral liquid: 150 mg/5 mL (as palmitate)
Chlorpromazine	Injection: 25 mg/mL (hydrochloride) in 2 mL ampoule Oral liquid: 25 mg/5 mL (hydrochloride)* Tablet: 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride)* *Oral formulations of chlorpromazine are now included as therapeutic alternatives under the square box listing for oral haloperidol (Section 24.1)
Dasabuvir	Tablet: 250 mg
Ethionamide	Tablet: 125 mg

Hydroxycarbamide	Solid oral dosage form: 250 mg
Linezolid	Powder for oral liquid: 100 mg/5 mL (Section 6.2.5) Tablet: 400 mg (Section 6.2.3)
Nifurtimox	Tablet: 250 mg
Nystatin	Tablet: 100 000 IU
Ombitasvir + paritaprevir + ritonavir	Tablet: 12.5 mg + 75 mg + 50 mg
p-aminosalicylic acid	Granules: 4 g in sachet
Paracetamol	Tablet: 100 mg
Pegylated interferon alfa (2a or 2b)	Vial or pre-filled syringe: 180 micrograms (peginterferon alfa 2a); 80 micrograms, 100 micrograms (peginterferon alfa 2b)
Pentamidine	Powder for injection: 200 mg (as isethionate) in vial
Phenytoin	Oral liquid: 25 mg/5 mL (phenytoin)
Pyrantel	Oral liquid: 50 mg/mL (as embonate or pamoate)

Table 2: Recommended changes on the 2023 EMLc

EMLc – New medicines added	
Medicine	**Indication**
Ansuvimab	Ebola virus disease
Atoltivimab + maftivimab + odesivimab	Ebola virus disease
Ceftolozane + tazobactam	Multidrug resistant bacterial infections
Cryoprecipitate, pathogen-reduced	Bleeding disorders
Deferasirox	Iron overload
Levetiracetam	Partial- and generalized-onset seizures, status epilepticus
Pegfilgrastim	Febrile neutropenia prophylaxis
Pegylated liposomal doxorubicin	Kaposi sarcoma
Ready-to-use therapeutic food	Severe acute malnutrition
Resin-based composites	Dental caries
Selenium sulfide	Seborrhoeic dermatitis, pityriasis versicolor
Sevoflurane	General anaesthesia
Triamcinolone hexacetonide	Juvenile idiopathic arthritis
EMLc - New indications	
Medicine	**Indication**
Cyclophosphamide	Anaplastic large cell lymphoma
Cytarabine	Anaplastic large cell lymphoma, Langerhans cell histiocytosis
Dexamethasone	Anaplastic large cell lymphoma
Doxorubicin	Anaplastic large cell lymphoma
Ethionamide	Drug-susceptible tuberculosis meningitis
Etoposide	Anaplastic large cell lymphoma
Ifosfamide	Anaplastic large cell lymphoma
Immunoglobulin	Langerhans cell histiocytosis
Mercaptopurine	Langerhans cell histiocytosis
Methotrexate	Anaplastic large cell lymphoma, Langerhans cell histiocytosis, psoriasis
Prednisolone	Anaplastic large cell lymphoma, Langerhans cell histiocytosis
Rituximab	Burkitt lymphoma
Vinblastine	Anaplastic large cell lymphoma, Langerhans cell histiocytosis
Vincristine	Langerhans cell histiocytosis
EMLc - New formulation/strength	
Medicine	**Formulation/strength**
Adalimumab	Injection: 10 mg/0.2 mL; 20 mg/0.4 mL
Albendazole	Tablet (chewable): 200 mg (Section 6.1.4)
Amikacin	Injection: 50 mg/mL (as sulfate) in 2 mL vial (Section 6.2.1)
Amoxicillin	Tablet (dispersible, scored): 250 mg; 500 mg (as trihydrate)
Amoxicillin + clavulanic acid	Tablet (dispersible): 200 mg (as trihydrate) + 28.5 mg (as potassium salt); 250 mg (as trihydrate) + 62.5 mg (as potassium salt)
Arsenic trioxide	Concentrate for solution for infusion: 2 mg/mL
Azathioprine	Oral liquid: 10 mg/mL Powder for injection: 50 mg (as sodium salt) in vial Tablet: 25 mg
Azithromycin	Powder for oral liquid: 200 mg/5 mL (anhydrous)

Calcium folinate	Injection: 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule
Carbamazepine	Tablet (scored): 400 mg
Cefalexin	Tablet (dispersible): 125 mg; 250 mg
Cefotaxime	Powder for injection: 500 mg; 1 g; 2 g (as sodium) in vial
Ceftriaxone	Powder for injection: 500 mg (as sodium) in vial
Ciclosporin	Oral solution: 100 mg/mL
Ciprofloxacin	Solid oral dosage form: 100 mg (as hydrochloride)
Clarithromycin	Solid oral dosage form: 250 mg
Clindamycin	Powder for oral liquid: 75 mg/5 mL (as palmitate hydrochloride)
Cloxacillin	Capsule: 250 mg Powder for injection: 250 mg (as sodium) in vial Powder for oral liquid: 250 mg/5 mL (as sodium)
Cytarabine	Injection: 100 mg/mL
Dacarbazine	Powder for injection: 200 mg in vial
Daunorubicin	Injection: 2 mg /mL; 5 mg/mL in vial Powder for injection: 20 mg in vial
Digoxin	Injection: 100 micrograms/mL in 1 mL ampoule Tablet: 125 micrograms
Doxorubicin	Injection: 2 mg/mL (hydrochloride) in 5 mL, 25 mL vial
Doxycycline	Powder for oral liquid: 25 mg/5 mL (monohydrate) Oral liquid: 50 mg/5 mL (calcium) Tablet (dispersible): 100 mg (as monohydrate)
Enalapril	Oral solution: 1 mg/mL (as hydrogen maleate) Tablet: 10 mg (as hydrogen maleate)
Etoposide	Powder for injection: 100 mg (as phosphate) in vial
Fluconazole	Powder for oral liquid: 50 mg/5 mL
Fluoride	Gel: containing 2500 to 12 500 ppm fluoride (any type) Mouthrinse: containing 230 to 900 ppm fluoride (any type) Varnish: containing 22 500 ppm fluoride (any type)
Furosemide	Injection: 10 mg/mL in 5 mL ampoule Oral liquid: 50 mg/5 mL Tablet: 20 mg
Hydroxycarbamide	Solid oral dosage form: 100 mg
Ibuprofen	Oral liquid: 100 mg/5 mL
Insulin injection (soluble)	Injection: 100 IU/mL in 3 mL cartridge or pre-filled pen.
Intermediate-acting insulin	Injection: 100 IU/mL in 3 mL cartridge or pre-filled pen.
Linezolid	Tablet (dispersible): 150 mg (Section 6.2.3)
Mebendazole	Tablet (chewable): 100 mg (Section 6.1.4)
Mercaptopurine	Oral liquid: 20 mg/mL
Methotrexate	Injection: 50 mg/2 mL (Section 8.2.1) Concentrated injection: 1000 mg/10 mL (Section 8.2.1)
Nifurtimox	Tablet (scored): 30 mg (Section 6.5.5.1)
Nitrofurantoin	Solid oral dosage form: 50 mg
p-aminosalicylate sodium	Powder for oral solution: 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid)
Paracetamol	Oral liquid: 250 mg/5 mL Suppository: 250 mg Tablet (dispersible): 100 mg; 250 mg

Pegaspargase	Powder for injection: 3,750 units in vial
Pentamidine	Powder for injection: 300 mg (as isethionate) in vial
Phenobarbital	Injection: 30 mg/mL or 60 mg/mL (sodium)
Praziquantel	Tablet: 150 mg (Section 6.1.3 & 6.1.4) Tablet: 500 mg (Section 6.1.1 & 6.1.3)
Rifampicin	Oral liquid: 20 mg/mL (Section 6.2.4)
Sulfamethoxazole + trimethoprim	Tablet (dispersible): 100 mg + 20 mg (Section 6.2.1 and 6.5.4)
Valproic acid (sodium valproate)	Injection: 100 mg/mL in 3 mL ampoule
Vancomycin (IV)	Powder for injection: 500 mg; 1 g (as hydrochloride) in vial
EMLc – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Amikacin	Injection: 100 mg/2 mL (as sulfate) in 2 mL vial (Section 6.2.5)
Azithromycin	Oral liquid: 200 mg/5 mL
Chloramphenicol	Capsule 250 mg Oral liquid: 150 mg/5 mL (as palmitate)
Chlorpromazine	Injection: 25 mg/mL (hydrochloride) in 2 mL ampoule Oral liquid: 25 mg/5 mL (hydrochloride) Tablet: 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride)
Clarithromycin	Solid oral dosage form: 500 mg
Clindamycin	Oral liquid: 75 mg/5 mL (as palmitate)
Dasatinib	Tablet: 100 mg; 140 mg
Doxycycline	Oral liquid: 25 mg/5 mL (anhydrous)
Ethambutol	Oral liquid: 25 mg/mL
Ethionamide	Tablet: 125 mg
Haloperidol	Injection: 5 mg in 1 mL ampoule Oral liquid: 2 mg/mL Solid oral dosage form: 0.5 mg; 2 mg; 5 mg
Fluoxetine	Solid oral dosage form: 20 mg (as hydrochloride) (Section 2.3 & 24.2.1)
Furosemide	Tablet: 10 mg
Hydroxycarbamide	Solid oral dosage form: 250 mg
Isoniazid	Oral liquid: 50 mg/5 mL
Levamisole	Tablet: 150 mg (as hydrochloride)
Linezolid	Powder for oral liquid: 100 mg/5 mL (6.2.5) Tablet: 400 mg; 600 mg (6.2.3)
Nifurtimox	Tablet: 250 mg
Nystatin	Oral liquid: 50 mg/5 mL Tablet: 100 000 IU
p-aminosalicylic acid	Granules: 4 g in sachet
Paracetamol	Tablet: 100 mg
Pentamidine	Powder for injection: 200 mg (as isethionate) in vial)
Phenytoin	Oral liquid: 25 mg/5 mL (phenytoin)
Pyrantel	Oral liquid: 50 mg/mL (as embonate or pamoate)
Pyrazinamide	Oral liquid: 30 mg/mL
Vinorelbine	Capsule: 80 mg

Table 3: Other changes on the 2023 EML and EMLc

Other changes to listings – EML and/or EMLc		
Albendazole	Add "(scored)" to listings for albendazole 400 mg chewable tablets	EML & EMLc
Amitriptyline	Remove square box	EML
Amphotericin B	Add note stating "Liposomal amphotericin B has a better safety profile than the deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost"	EML & EMLc
Azithromycin	Replace "capsule" with "solid oral dosage form"	EML & EMLc
Bedaquiline	Remove age restriction	EML & EMLc
Benznidazole	Add "(scored)" to listings of benznidazole 50 mg and 100 mg tablets	EML & EMLc
Bleomycin	Modify strength description from 15 mg to 15 000 IU	EML & EMLc
Calcium folinate	Include the alternative medicine name "leucovorin calcium" in the listing	EML & EMLc
Clofazimine	Replace "capsule" with "solid oral dosage form"	EML & EMLc
Colistin	Add equivalent strength in colistin base activity	EML & EMLc
Cyclophosphamide	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Deferoxamine	Remove square box	EML & EMLc
Delamanid	Remove age restriction	EML & EMLc
Diazepam	Modify listing for rectal formulations for use in status epilepticus to better describe available dosage forms (Section 2.3 & 5.1)	EML & EMLc
Diazepam	Specify lorazepam as therapeutic alternative and add note stating "For short-term emergency management of acute and severe anxiety symptoms only" (Section 24.3)	EML
Digoxin	Transfer listing from the core to the complementary list	EMLc
Eflornithine	Amend bottle size from 100 mL to 50 mL	EML & EMLc
Fluphenazine	Therapeutic alternatives specified as haloperidol decanoate and zuclopenthixol decanoate	EML
Fluorouracil	Remove specification of vial size	EML & EMLc
Haloperidol	Therapeutic alternatives specified as chlorpromazine (oral formulations only)	EML
Hydroxycarbamide	Include the alternative medicine name "hydroxyurea" in the listing	EML & EMLc
Ivermectin	Remove "(scored)" from listings for ivermectin 3 mg tablets	EML & EMLc
Linezolid	Add square box specifying tedizolid as a therapeutic alternative for infections caused by multidrug-resistant organisms (Section 6.2.3)	EML
Metronidazole	Replace tablet formulation strength range with specific strengths	EML & EMLc
Midazolam	Modify listings for use in status epilepticus to better describe available dosage forms.	EML & EMLc
Nifurtimox	Add "(scored)" to listings of nifurtimox 30 mg and 120 mg tablets	EML & EMLc
Nitrofurantoin	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Nystatin	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Paracetamol	Include the alternative medicine name "acetaminophen" in the listing Replace tablet formulation strength range with specific strengths Add note stating "The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusing in prescribing and dispensing and should be avoided"	EML & EMLc
Phenoxymethylpenicillin	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Phenytoin	Specify salt or free acid form for all formulations; remove reference to vial size for 50 mg/mL injection formulation.	EML & EMLc
Polymyxin B	Include equivalent strength in mg of polymyxin B base	EML & EMLc
Praziquantel	Add "(scored)" to listings for praziquantel 600 mg tablets	EML & EMLc

Risperidone	Add square box specifying aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives for schizophrenia and related psychoses.	EML
Sodium stibogluconate or Meglumine antimoniate	List each medicine separately	EML & EMLc
Triclabendazole	Add "(scored)" to listings for triclabendazole 250 mg tablets	EML & EMLc
Vancomycin (oral)	Add note stating "vancomycin powder for injection may also be used for oral administration"	EML & EMLc
Vecuronium	Include atracurium as a therapeutic alternative under the square box listing of vecuronium	EMLc
Vinorelbine	Modify listing to read 10 mg/mL in 1 mL or 5 mL vial	EML & EMLc

Changes to sections and sub-sections

	2021	**2023**
Section 5	Anticonvulsants/antiepileptics	Medicines for diseases of the nervous system
Section 5.1	N/A	Antiseizure medicines
Section 5.2	N/A	Medicines for multiple sclerosis
Section 5.3	N/A	Medicines for parkinsonism
Section 6.7	N/A	Medicines for Ebola virus disease
Section 6.8	N/A	Medicines for COVID-19
Section 9	Antiparkinsonism medicines	Therapeutic foods
Section 12.7	N/A	Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease
Section 18.8	N/A	Medicines for disorders of the pituitary hormone system
Section 24.5.1	N/A	Medicines for alcohol use disorders
Section 24.5.2	N/A	Medicines for nicotine use disorders
Section 24.5.3	N/A	Medicines for opioid use disorders
Section 30	Dental preparations	Dental medicines and preparations

Table 4: Applications not recommended

ADDITIONAL MEDICINES	
Addition of alfacalcidol and calcitriol for treatment of disorders of bone and calcium metabolism	EML & EMLc
Addition of anakinra for treatment of systemic onset juvenile idiopathic arthritis with macrophage activation syndrome	EML & EMLc
Addition of CD-19-directed antigen receptor (CAR) T cells (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) for treatment of relapsed or refractory large B-cell lymphoma	EML
Addition of cladribine for treatment of refractory Langerhans cell histiocytosis	EMLc
Addition of crizotinib for treatment of relapsed/refractory anaplastic large cell lymphoma	EMLc
Addition of cyclin-dependent kinase 4/6 inhibitors (abemaciclib, palbociclib, ribociclib) for treatment of hormone receptor positive/HER2-negative advanced or metastatic breast cancer	EML
Addition of donepezil for treatment of Alzheimer disease dementia	EML
Addition of estradiol for induction of puberty	EML
Addition of flomoxef sodium for empiric treatment of community acquired mild/moderate intraabdominal and upper urinary tract infections	EML & EMLc
Addition of glucagon-like peptide-1 receptor antagonists for treatment of obesity	EML
Addition of hypromellose for treatment of dry eye disease	EML & EMLc
Addition of imipenem + cilastatin + relebactam for treatment of bacterial infections due to multidrug-resistant organisms	EML & EMLc
Addition of ketoconazole for treatment of Cushing syndrome	EML
Addition of ocrelizumab for treatment of multiple sclerosis	EML
Addition of osimertinib for treatment of EGFR-mutation positive advanced or metastatic non-small cell lung cancer	EML
Addition of PD-1/PD-L1 immune checkpoint inhibitors (pembrolizumab, atezolizumab, cemiplimab, durvalumab) for non-oncogene addicted locally advanced or metastatic non-small cell lung cancer	EML
Addition of phenelzine for treatment of treatment-resistant depression	EML
Addition of phosphorus for treatment of hypophosphataemic rickets	EMLc
Addition of recombinant coagulation factors or bypassing agents as therapeutic alternatives to plasma-derived coagulation factors	EML & EMLc
Addition of risdiplam for treatment of spinal muscular atrophy	EML & EMLc
Addition of somatropin for management of hypoglycaemia secondary to growth hormone deficiency	EMLc
Addition of sunscreen for prevention of skin cancer in people with albinism or xeroderma pigmentosum	EML & EMLc
Addition of ticagrelor for prevention of atherothrombotic events	EML
Addition of tislelizumab for treatment of non-oncogene addicted locally advanced and metastatic non-small cell lung cancer	EML
Addition of tocilizumab for treatment of systemic onset juvenile idiopathic arthritis	EML & EMLc
Addition of toripalimab for treatment of locally advanced or metastatic nasopharyngeal and oesophageal cancers	EML
Addition of ustekinumab for treatment of severe psoriasis	EML
Addition of zanubrutinib for treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma	EML
NEW FORMULATIONS / STRENGTHS	
Oral transmucosal formulations of fentanyl citrate for treatment of breakthrough cancer pain	EML
Methotrexate sub-cutaneous injection for severe inflammatory conditions	EML & EMLc
Paliperidone palmitate 3-month long-acting injection for maintenance treatment of schizophrenia	EML
NEW INDICATIONS	
New indication for zoledronic acid for treatment of osteogenesis imperfecta	EML & EMLc