World Health Organization

REGIONAL OFFICE FOR Europe

Changes to 2019 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc)

This summary has been prepared by the Health Technologies and Pharmaceuticals (HTP) programme at the WHO Regional Office for Europe.

It is intended to communicate changes to the WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc) to national counterparts involved in the evidence-based selection of medicines for inclusion in national essential medicines lists (NEMLs), lists of medicines for inclusion in reimbursement programs, and medicine formularies for use in primary, secondary and tertiary care.

This document does not replace the full report of the WHO Expert Committee on Selection and Use of Essential Medicines (see The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021). Licence: CC BY-NC-SA 3.0 IGO: https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1) and Corrigenda (March 2020) – TRS1021 (https://www.who.int/medicines/publications/essentialmedicines/TRS1021_corrigenda_March2020.pdf?ua=1) and this Executive summary (https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?ua=1).

The revised lists of essential medicines are available here:

- World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1).

- World Health Organization Model List of Essential Medicines for Children, 7th List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1).

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Introduction

This summary reports the recommendations made by the WHO Expert Committee on the Selection and Use of Essential Medicines for the 2019 Essential Medicines Lists update.

The 22nd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Geneva, Switzerland, from 1 to 5 April 2019. The aim of the meeting was to review and update the 20th WHO Model List of Essential Medicines (EML) and the 6th WHO Model List of Essential Medicines for Children (EMLc).

The Expert Committee considered 65 applications, including proposals to add 53 new medicines and new formulations of 19 existing medicines, extend the indications for 34 listed medicines, and to remove 10 medicines or formulations from the lists. The Expert Committee also considered reports and recommendations from the EML Antibiotics and Cancer Medicines Working Groups. In accordance with applicable procedures[1], the Expert Committee evaluated the scientific evidence for the comparative effectiveness, safety and cost-effectiveness of the medicines in question.

In summary, the Expert Committee:

- recommended the addition of 28 new medicines to the EML (12 to the core list and 16 to the complementary list);
- recommended the addition of 23 new medicines to the EMLc (6 to the core list and 17 to the complementary list);
- recommended the addition of new formulations of 16 currently listed medicines;
- recommended adding additional indications for 26 currently listed medicines;
- recommended the deletion of 9 medicines and of specific formulations of a further 4 medicines; and
- rejected 21 applications for inclusion, change or deletion of 31 medicines.

A summary of these changes is shown in Table 1.

Tables showing the *additions* to the EML and EMLc, both new medicines and new formulations of existing medicines, along with additional indications for currently listed medicines (Table 2) and rejected applications (Table 3) are included in an annex to this summary.

A detailed summary of the 2019 revisions to the Access, Watch and Reserve (AWaRe) classification of antibiotics is provided in a separate document. Section 6 of the EML and EMLc have been restructured to align with the AWaRe classification.

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

Section 8 has been renamed *Immunomodulators and antineoplastics.* A separate document summarises the changes to Section 8 in 2019 and reports on the considerations of the Cancer Medicines Working Group to establish criteria for the inclusion of medicines on the EML and EMLc based on a threshold for benefit.

Ensuring affordable access to insulin remains a challenge for patients and health systems in the European Region. A separate document summarises the considerations of the Expert Committee in 2019 regarding analogue insulins.

Table 1 Summary of all changes to 2019 WHO EML and EMLc

Section	Medicine	EML, EMLc
Section 1: Anaesthetics, preoperative medicines and medical gases		
	No changes	
Section 2: Medicines for pain and palliative care		
	No changes	
Section 3: Antiallergics and medicines used in anaphylaxis		
	No changes	
Section 4: Antidotes and other substances used in poisonings		
	No changes	
Section 5: Anticonvulsants/antiepileptics		
	No changes	
Section 6: Anti-infective medicines (restructured sections to align AWaRe categorisation)		
6.2	*See separate summary of changes to AWaRe classification section 6.2* – **6.2.1: Access group antibiotics** – **6.2.2: Watch group antibiotics** – **6.2.3: Reserve group antibiotics** – **6.2.4: Antileprosy medicines** – **6.2.5: Antituberculosis medicines**	
	New indications for existing medicines on EML and EMLc *Typhoid and paratyphoid (enteric) fever* Ciprofloxacin (Watch) Ceftriaxone (Watch) Azithromycin (Watch) ***Rejected*** *listing for ofloxacin* *Surgical prophylaxis* Cefazolin (Access) Cefazolin (Access) + metronidazole (Access) Amoxicillin + clavulanic acid (Access) + gentamicin (Access) *Oral and dental infections* Amoxicillin (Access) Phenoxymethylpenicillin (Access)	EML, EMLc

Section	Medicine	EML, EMLc
6.2.2	Cefuroxime (surgical prophylaxis – Watch)	EML, EMLc
6.2.3	Ceftazidime + avibactam (Reserve last-resort antibiotic)	EML
	Meropenem + vaborbactam (Reserve last-resort antibiotic)	EML
	Plazomicin (Reserve last-resort antibiotic)	EML
	Rejected Ceftolozone + tazobactam as last-resort antibiotic	
	Rejected Delafloxacin as last-resort antibiotic	
	Rejected Eravacycline as last-resort antibiotic	
	Rejected Omadacycline as last-resort antibiotic	
6.2.5	***Anti-tuberculosis medicines - new dispersible tablet formulations*** Cycloserine Ethambutol Ethionamide Isoniazid Levofloxacin Linezolid Moxifloxacin Clofazimine Rifabutin	EMLc
	Deletion ethambutol + isoniazid 400mg+150mg (fixed-dose combination)	EML
	Deletion isoniazid + pyrazinamide + rifampicin 150mg+500mg+150mg (fixed-dose combination)	EML
	Deletion Isoniazid + rifampicin 60mg+60mg and 150mg+150mg (fixed-dose combination)	EML
	Rejected *application for addition of injection formulations* Ethambutol Isoniazid p-aminosalicylic acid Rifampicin	
	Bedaquiline (MDR-TB in children and adolescents 6-17 years)	EMLc
	Deletion capreomycin (MDR-TB)	EML, EMLc
	Deletion kanamycin (MDR-TB)	EML, EMLc
	Rejected change to age restriction for delamanid (remains 6-17 years)	EMLc
	New indication Amoxicillin + clavulanic acid (multidrug-resistant TB)	EML, EMLc
	New indication Meropenem (multidrug-resistant tuberculosis, MDR-TB) Imipenem + cilastatin may be an alternative (multidrug-resistant TB)	EML, EMLc
	Rejected Isoniazid liquid (tuberculosis infants, children)	EMLc
	Isoniazid 100mg dispersible tablet (tuberculosis infants, children)	EMLc
6.4.2	***Deletion*** Zidovudine: tablet (dispersible, scored) 60 mg	EML, EMLc
	Deletion Abacavir + lamivudine: tablet (dispersible, scored) 60 mg+30 mg	EML, EMLc
	Retain Ritonavir: oral liquid 400 mg / 5 mL	EML, EMLc
	Retain Raltegravir: tablet (chewable) 100 mg	EML, EMLc
	Dolutegravir + lamivudine + tenofovir disoproxil fumarate (fixed-dose combination)	EML
6.4.2.3	Ritonavir oral powder 100mg	EML, EMLc
	Lopinavir + ritonavir oral granules 40 mg + 10 mg fixed-dose combination	EMLc

Section	Medicine	EML, EMLc
6.4.2.4	Dolutegravir 50mg tablet (for children weighing 25kg or more)	EMLc
	Raltegravir granules for oral suspension 100 mg	EML, EMLc
6.4.4.2	*Medicines for hepatitis C now differentiates between pangenotypic and non-pangenotypic direct acting antivirals, and other antivirals*	
6.4.4.2.1	*Pangeotypic direct-acting antiviral combinations* Glecaprevir + pibrentasvir This new combination adds to existing pagenotypic combination options on the EML (sofosbuvir + velpatasvir, sofosbuvir/daclatasvir)	EML
	Non-pangeotypic direct-acting antiviral combinations ***Deletion*** simeprevir	EML
6.5.3.2	Sulfadoxine + pyrimethamine (fixed-dose combination; intermittent preventive treatment of malaria in pregnancy (IPTp))	EML
	Sulfadoxine + pyrimethamine (fixed-dose combination; intermittent preventive treatment of malaria in infancy (IPTi))	EMLc
	Amodiaquine and sulfadoxine + pyrimethamine (co-packaged formulations of dispersible tablets; for seasonal malaria chemoprevention)	EMLc
6.5.5.1	Fexinidazole for treatment of 1st and 2nd stages of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.	EML, EMLc
6.6	*Medicines for ectoparasitic infections (new section)* Ivermectin (scabies)	EML, EMLc
Section7: Antimigraine medicines		
	Rejected sumitriptan	EML
Section 8: (Re-named) Immunomodulators and antineoplastics		
8.1	***Rejected*** glatiramer acetate (multiple sclerosis)	
	Rejected fingolimod (multiple sclerosis)	
	Rejected ocrelizumab (multiple sclerosis)	
	Anti-TNF biologics for chronic inflammatory conditions Adalimumab *Listed with square box with nominated alternatives:* Etanercept, infliximab, certolizumab pegol and golimumab (adults) Etanercept, infliximab (children)	EML, EMLc EML EMLc
8.2	***Re-named Antineoplastic and supportive agents***	
	All-trans retinoid acid (Acute promyelocytic leukaemia)	EMLc
	Dasatinib (Imatinib-resistant chronic myeloid leukaemia)	EMLc
	Fluorouracil (nasopharyngeal carcinoma, early-stage colon cancer, early-stage rectal cancer, metastatic colorectal cancer)	EMLc
	Imatinib (chronic myeloid leukaemia, gastrointestinal stromal tumour)	EMLc
	Irinotecan (metastatic colorectal cancer)	EMLc
	Nilotinib (imatinib-resistant chronic myeloid leukaemia)	EMLc
	Oxaliplatin (early stage colon cancer, metastatic colorectal cancer)	EMLc
	Procarbazine (Hodgkin lymphoma)	EMLc
	Rituximab (diffuse large B-cell lymphoma)	EMLc
	Enoxaparin (anticoagulant) *Listed with a square box*	EMLc

Section	Medicine	EML, EMLc
	Extension of indications for currently listed cancer medicines for children Bleomycin (Kaposi sarcoma) Doxorubicin (Kaposi sarcoma) Vincristine (Kaposi sarcoma) Cisplatin (Nasopharyngeal carcinoma) Cyclophosphamide (Diffuse large B-cell lymphoma) Prednisolone (Diffuse large B-cell lymphoma) Cytarabine (Acute promyelocytic leukaemia) Daunorubicin (Acute promyelocytic leukaemia) Mercaptopurine (Acute promyelocytic leukaemia) Methotrexate (Acute promyelocytic leukaemia) Cytarabine (Acute myelogenous leukaemia) Hydroxycarbamide (Chronic myeloid leukaemia)	EMLc
	Rejected zoledronic acid	
8.2.1	Arsenic trioxide (IV formulations; acute promyelocytic leukaemia)	EML, EMLc
	Realgar-Indigo naturalis (containing tetra-arsenic tetra sulphide 30mg; acute promyelocytic leukaemia)	EML, EMLc
	Extension of indications for currently listed cancer medicines Cisplatin (cervical cancer) Carboplatin (cervical cancer) Paclitaxel (cervical cancer)	EML
	Rejected Fluorouracil (cervical cancer)	
	Pegaspargase (acute lymphoblastic leukaemia)	EML, EMLc
	Additional indication cyclophosphamide (multiple myeloma)	EML
	Additional indication doxorubicin (multiple myeloma)	EML
8.2.2	***Rejected*** pertuzumab (HER-2 positive breast cancer)	
	Rejected subcutaneous formulation of rituximab (diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma)	
	Rejected subcutaneous formulation of trastuzumab (HER-2 positive breast cancer)	
	Rejected trastuzumab emtansine (HER-2 positive breast cancer)	
	Erlotinib (EGFR mutation positive advanced non-small cell lung cancer) *Listed with square box with nominated alternatives:* afatinib, gefitinib	EML
	Bortezomib (multiple myeloma)	EML
8.2.3	Lenalidomide (multiple myeloma)	EML
	Thalidomide (multiple myeloma)	EML
	Melphalan (multiple myeloma)	EML
	Nivolumab (metastatic melanoma). *Listed with square box with nominated alternative:* pembrolizumab	EML
	Rejected atezolizumab (metastatic non-small cell lung cancer)	
	Rejected nivolumab (metastatic non-small cell lung cancer)	
	Rejected pembrolizumab (metastatic non-small cell lung cancer)	
8.2.4	Abiraterone (metastatic castration-resistant prostate cancer)	EML
	Rejected Enzalutamide (metastatic castration-resistant prostate cancer)	

Section	Medicine	EML, EMLc
	Additional indication prednisone (multiple myeloma)	EML
	Additional indication dexamethasone (multiple myeloma)	EML
Section 9: Antiparkinsonism medicines		
	No changes	
Section 10: Medicines affecting the blood		
10.2	Dabigatran *Listed with square box with nominated alternatives:* apixaban, edoxaban, rivaroxaban	EML
Section 11: Blood products of human origin and plasma substitutes		
	No changes	
Section 12: Cardiovascular medicines		
12.3	Lisinopril + amlodipine (fixed-dose combination) *Listed with square box for ACE inhibitors (lisinopril) and dihydropyridine class of calcium channel blockers (amlodipine)*	EML
	Lisinopril + hydrochlorothiazide (fixed-dose combination) *Listed with square box for ACE inhibitors (lisinopril) and thiazide diuretics (hydrochlorothiazide)*	EML
	Telmisartan + amlodipine (fixed-dose combination) *Listed with square box for angiotensin receptor antagonists (telmisartan) and dihydropyridine class of calcium channel blockers (amlodipine)*	EML
	Telmisartan + hydrochlorothiazide (fixed-dose combination) *Listed with square box for angiotensin receptor antagonists (telmisartan) and thiazide diuretics (hydrochlorothiazide)*	EML
12.5.2	Alteplase (acute ischaemic stroke)	EML
Section 13: Dermatological medicines (topical)		
	No changes	
Section 14: Diagnostic agents		
	No changes	
Section 15: Disinfectants and antiseptics		
	No changes	
Section 16: Diuretics		
	No changes	
Section 17: Gastrointestinal medicines		
17.2	Aprepitant (chemotherapy-induced nausea and vomiting)	EML, EMLc
	Ondansetron *listed with square box with nominated alternatives: other 5-HT3 receptor antagonists*	EML, EMLc
17.5	Oral rehydration salts and zinc sulfate tablets (co-packaged)	EMLc
Section 18: Re-named Medicines for endocrine disorders		
18.5	***Rejected*** Long-acting insulin analogues (including biosimilars)	
18.6	Diazoxide (hypoglycaemia secondary to prolonged hyperinsulinism)	EMLc
18.7	Methimazole (hyperthyroidism) *Listed with square box with nominated alternative:* carbimazole	EML, EMLc
	Remove square box listing for propylthiouracil	EML
Section 19: Immunologicals		

Section	Medicine	EML, EMLc
19.3	*Vaccines* Dengue vaccine	EML, EMLc
Section 20: Muscle relaxants (peripherally-acting) and cholinesterase inhibitors		
	No changes	
Section 21: Ophthalmological preparations		
	No changes	
Section 22: Re-named Medicines for reproductive health and perinatal care		
22.3	Carbocetin (prevention of post-partum haemorrhage)	EML
	Retain Misoprostol (prevention of post-partum haemorrhage)	
	Mifepristone and misoprostol ***Moved*** to Core List; ***Removal*** of the note "Requires close medical supervision; ***Addition*** of co-packaged presentation	EML
22.5	Tranexamic acid (post-partum haemorrhage)	EML
Section 23: Peritoneal dialysis solution		
	No changes	
Section 24: Medicines for mental and behavioural disorders		
	Rejected methylphenidate (attention-deficit hyperactivity disorder, ADHD)	
24.2.1	***Rejected*** escitalopram	
	Fluoxetine *Listed with square box* (depressive disorders)	EML
Section 25: Medicines acting on the respiratory tract		
25.1	Tiotropium *Listed with square box* for long-acting muscarinic agents (chronic obstructive pulmonary disease)	EML
Section 26: Solutions correcting water, electrolyte and acid–base disturbances		
	No changes	
Section 27: Vitamins and minerals		
	Iodine *Corrected listed strength to 190mg*	
	Multiple micronutrient powders (prevention of anaemia in infants and children)	EMLc
Section 28: Ear, nose and throat medicines		
	No changes	
Section 29: Re-named Medicines for diseases of joints		
	No changes	
Section 30: Deleted Medicines for diseases of joints		

Section 1: Anaesthetics, preoperative medicines and medical gases

No changes

Section 2: Medicines for pain and palliative care

No changes

Section 3: Antiallergics and medicines used in anaphylaxis

No changes

Section 4: Antidotes and other substances used in poisonings

No changes

Section 5: Anticonvulsants/antiepileptics

No changes

Section 6: Anti-infective medicines (restructured to align with the 2019 AWaRe categorisation)

6.2: Antibacterials

Typhoid and paratyphoid (enteric) fever

NEW INDICATION: The Expert Committee endorsed listing of ciprofloxacin, ceftriaxone and azithromycin as first-choice treatments for typhoid and paratyphoid (enteric) fever on the core list of the EML and EMLc. Ciprofloxacin is recommended as first-choice in settings with low prevalence of fluoroquinolone resistance, while ceftriaxone and azithromycin are recommended first-choice treatments in settings where there is a high prevalence of fluoroquinolone resistance.

Ciprofloxacin, azithromycin and ceftriaxone are all classified as Watch group antibiotics (Section 6.2.2).

REJECTED APPLICATION: Following the principle of parsimony, the Expert Committee did not recommend the addition of ofloxacin for this indication, noting that ofloxacin and ciprofloxacin have demonstrated similar clinical performance for this indication in clinical trials.

Antibiotics for surgical prophylaxis

NEW INDICATION: The Expert Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion. In line with previous decisions for infectious syndromes, alternatives for use in case of allergy were not recommended.

The Expert Committee endorsed listing of cefazolin, alone or in combination with metronidazole as first-choice options, and of amoxicillin + clavulanic acid and gentamicin as second-choice options for surgical prophylaxis on the core list of the EML and EMLc, as Access group antibiotics (Section 6.2.1).

ADDITION: The Committee also recommended the addition of cefuroxime to the core list of the EML and EMLc as a second-choice option for surgical prophylaxis, as a Watch group antibiotic (Section 6.2.2), as an alternative to cefazolin.

Antibiotics for oral and dental infections

NEW INDICATION: The Expert Committee endorsed listing of amoxicillin and phenoxymethylpenicillin on the core list of the EML and EMLc as first-choice treatment for progressive (systemically complicated) apical dental abscess. These antibiotics are also recommended as first-choice treatment of apical dental abscess in medically compromised patients.

Amoxicillin and phenoxymethylpenicillin are classified as Access group antibiotics (Section 6.2.1).

6.2.1: Access group antibacterials

6.2.2: Watch group antibacterials

6.2.3: Reserve group antibacterials

Ceftazidime + avibactam – last-resort antibiotic for infections due to multi-drug resistant organisms – EML (ATC Code: J01DD52)

ADDITION: The Expert Committee recommended the inclusion of ceftazidime + avibactam on the complementary list of the EML and EMLc for the treatment of infections caused by carbapenem-resistant organisms which are pathogens classified as "critical priority" in the WHO Priority Pathogen List.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group.

The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health orientated studies that will help to inform the choice of optimal single or combination treatment of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

Ceftolozane + tazobactam – <u>rejected</u> application as last-resort antibiotic for infections due to multi-drug resistant organisms – EML (ATC Code: J01DI54)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of ceftolozane + tazobactam to the EML. The Committee noted that although ceftolozane + tazobactam is active against some strains of carbapenem-resistant *P. aeruginosa*, it lacks activity against carbapenemase-producing *Enterobacteriaceae,* which is more prevalent in the community and represents a greater public health threat. Alternative antibiotics are included on the list that are effective against carbapenem-resistant *P. aeruginosa*.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group.

Delafloxacin – rejected application as last-resort treatment option for infections due to multi-drug resistant organisms – EML (ATC Code J01MA23)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of delafloxacin to EML. The Committee noted that although delafloxacin has demonstrated activity against some MRSA strains ranked as "high priority" on the WHO Priority Pathogens List, effective alternatives are currently available on the EML. In addition, delafloxacin was not associated with greater activity against "critical priority" pathogens compared to other, older fluoroquinolones currently available on the Model List.

The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Watch group.

Eravacycline – rejected application as last-resort treatment option for infections due to multi-drug resistant organisms – EML (ATC Code J01AA13)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of eravacycline to the EML. The Committee considered that although eravacycline demonstrates activity against some strains of carbapenemase-producing *Enterobacteriaceae*, there are some concerns with regard to efficacy, as eravacycline failed to demonstrate non-inferiority compared to levofloxacin in one RCT for complicated UTI. In addition, the Committee considered that there could be safety concerns, with no long-term safety data currently available. The Committee noted pharmacological similarities between eravacycline and tigecycline, and the reported increased mortality associated with tigecycline in some meta-analyses.

The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that eravacycline be classified in the AWaRe Reserve group.

Meropenem + vaborbactam – last-resort antibiotic for infections due to multi-drug resistant organisms – EML (ATC Code J01DH52)

ADDITION: The Expert Committee recommended the inclusion of meropenem + vaborbactam on the complementary list of the EML for the treatment of infections caused by carbapenem-resistant organisms which are pathogens classified as "critical priority" in the WHO priority pathogen list.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group.

The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health orientated studies that will help to inform the choice of optimal single or combinations of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

Omadacycline – rejected application as last-resort treatment option for infections due to multi-drug resistant organisms – EML (ATC code to be assigned)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of omadacycline to the EML. The Committee considered that although omadacycline demonstrates activity against both Gram-positive and Gram-negative pathogens, including MRSA, available data for its effectiveness and safety are currently limited. The Committee noted the finding of potentially increased mortality associated with omadacycline in one RCT of patients with community-acquired pneumonia.

The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that omadacycline be classified in the AWaRe Reserve group.

Plazomicin – last-resort antibiotic for infections due to multi-drug resistant organisms – EML (ATC Code: to be assigned)

ADDITION: The Expert Committee recommended the inclusion of plazomicin on the complementary list of the EML for the treatment of infections caused by carbapenem-resistant organisms that are classified as "critical priority" in the WHO priority pathogen list.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group (Section 6.2.3).

The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health-orientated studies that will help to inform the choice of optimal single or combinations of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

6.2.4: Antileprosy medicines

6.2.5: Antituberculosis medicines

Antituberculosis medicines – new formulations (dispersible tablets) – EMLc

Cycloserine (ATC Code J04AB01)
Ethambutol (ATC Code J04AK02)
Ethionamide (ATC Code J04AD03)
Isoniazid (ATC Code J04AC01)

Levofloxacin (ATC Code J01MA12) Linezolid (ATC Code J01XX08) Moxifloxacin (ATC Code J01MA14) Clofazimine (ATC Code J04BA01) Rifabutin (ATC Code J04AB04)
ADDITION: The Expert Committee recommended the addition of the proposed dispersible tablet formulations of ethambutol and isoniazid to the core list of the EMLc, and of cycloserine, ethionamide, levofloxacin, linezolid and moxifloxacin to the complementary list of the EMLc for the treatment of children with drug-sensitive and drug-resistant TB. The Committee considered that the availability of quality-assured, age-appropriate formulations will help improve access to effective treatment for children with TB. The Committee also recommended the requested amendments to the dosage form terminology for clofazimine and rifabutin.

Antituberculosis medicines – formulations for deletion – EML

Ethambutol + isoniazid 400mg+ 150mg (ATC Code J04AM03) Isoniazid + pyrazinamide + rifampicin 150mg+500mg+150mg (ATC Code J04AM05) Isoniazid + rifampicin 60mg+60mg and 150mg+150mg (ATC Code J04AM02)
DELETION: The Expert Committee recommended the deletion of the proposed formulations from the core list of the EML, noting the advice of the WHO Global TB Programme department that their use is no longer recommended in current WHO guidelines based on evidence that treatment regimens involving these formulations have been associated with greater rates of treatment failure, relapse, mortality and acquired drug resistance.

Antituberculosis medicines – rejected application for addition of intravenous formulations – EML and EMLc

Ethambutol (ATC Code J04AK02) Isoniazid (ATC Code J04AC01) p-aminosalicylic acid (ATC Code J04AA01) Rifampicin (ATC Code J04AB02)
REJECTED APPLICATION: The Expert Committee did not recommend the addition of injectable formulations of ethambutol, isoniazid, p-aminosalicylic acid (PAS) and rifampicin to the EML and EMLc for treatment of drug susceptible TB in combination with other first-line medicines. The Committee noted that WHO guidelines recommend use of oral, preferably fixed-dose combination therapy for TB, but acknowledged that parenteral administration of TB medicines may be useful in a small number of critically unwell patients unable to tolerate oral therapy or patients with TB meningitis. The Committee considered that the inclusion of these parenteral TB formulations on the EML could result in inappropriate use of parenteral therapy in patients otherwise able to take oral therapy. The Committee also noted that the global market availability of these products was limited, and the comparative cost unknown.

Bedaquiline – multidrug-resistant tuberculosis in children aged 6 years and older – EMLc (ATC Code J04AK05)

ADDITION: The Expert Committee recommended the addition of bedaquiline to the complementary list of the EMLc for the treatment of MDR-TB in children aged 6 years and older, in line with updated WHO treatment guidelines. The Committee noted that the extrapolation of evidence from adult data to children suggested therapeutic bedaquiline exposure in children and no increased safety risk.

Capreomycin injection (ATC Code J04AB30) and kanamycin injection (ATC Code J01GB04) – deletion – EML and EMLc

DELETION: The Expert Committee recommended the deletion of capreomycin and kanamycin from the complementary list of the EML and EMLc, noting the advice of the WHO Global TB Programme that their use is no longer recommended in WHO guidelines due to evidence that regimens involving these agents were associated with worse outcomes compared with regimens that did not include them, and that fully oral regimens should be preferred for most patients.

Delamanid – rejected application to change age restriction – EMLc

REJECTED APPLICATION: The Expert Committee did not recommend the requested change to the age restriction that applies to the listing of delamanid on the Model Lists. The Committee noted that pharmacokinetic data used to inform the guideline development process used a different formulation of delamanid to that which is currently included on the Model Lists, which is not commercially available at this time, nor has it been demonstrated to be bioequivalent to the available, listed formulation.

Group C antibiotics for MDR-TB – new indication – EML and EMLc

Amoxicillin + clavulanic acid (ATC Code J01CR02)
Imipenem + cilastatin (ATC Code J01DH51)
Meropenem (ATC Code J01CR02)

NEW INDICATION: The Expert Committee recommended the inclusion of meropenem and of amoxicillin + clavulanic acid on the complementary list of the EML and EMLc for the new indication of use in the treatment of MDR-TB. The Committee recommended that imipenem + cilastatin could be considered as an alternative to meropenem for use in adults, and that the EML should note this accordingly.

The Committee noted the limited clinical evidence base, and the very low certainty in the estimates of effect associated with the carbapenems in MDR-TB treatment regimens. However, the Committee accepted the public health need for effective treatments for MDR-TB and considered that the updated WHO guideline recommendations would be supported by the inclusion of these medicines on the EML.

The Committee expressed some concern in relation to increased use of carbapenem antibiotics in the empiric treatment of MDR-TB and the development of carbapenem resistance and recommended that ongoing monitoring for the development of resistance be undertaken.

Isoniazid – rejected application for new formulation (oral liquid) – EMLc (ATC Code J04AC01)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of a new strength formulation of isoniazid oral liquid to the core list of the EMLc for treatment and preventive therapy of tuberculosis in infants and children. The Committee considered that quality-assured dispersible tablet formulations of TB medicines represent a preferred treatment option to oral liquid formulations. The Committee considered that an additional strength oral liquid formulation of isoniazid would be unlikely to add value to patients or TB treatment programmes.

ADDITION NEW FORMULATION: In addition, with the separate recommendation made at this meeting to add isoniazid 100 mg dispersible tablets to the EMLc, the Committee recommended that the existing isonidazid oral liquid formulation (50 mg/mL) could be considered for removal from the EMLc in 2021.

6.4.2: Antiretrovirals

Antiretrovirals - formulations for deletion – EML and EMLc

Zidovudine: tablet (dispersible, scored) 60 mg
Abacavir + lamivudine: tablet (dispersible, scored) 60 mg (as sulfate) + 30 mg

DELETION: The Committee recommended deletion of zidovudine 60 mg dispersible scored tablet and of abacavir + lamivudine 60 mg + 30 mg dispersible scored tablet from the EML and EMLc, noting they are no longer included in the current WHO Guidelines for paediatric HIV treatment, and that suitable alternatives are already included on the Model Lists and available for use.

Antiretrovirals - formulations to be retained – EML and EMLc

Ritonavir: oral liquid 400 mg/5 mL
Raltegravir: tablet (chewable) 100 mg

RETAIN: The Committee recommended that ritonavir oral liquid and raltegravir 100 mg chewable tablets be retained on the Model Lists at this time. The Committee considered that until the availability is well established of the alternative formulations of these medicines recommended in separate applications to this meeting, (ritonavir 100 mg oral powder and raltegravir 100 mg oral granules), deletion of the existing formulations could be premature.

The existing formulations could be flagged for deletion without further discussion in 2021 unless an application is received in support of their retention.

*Ritonavir – new formulation – EML and EMLc (*ATC Code J05AE03)

NEW FORMULATION: The Expert Committee recommended the addition of the new formulation of ritonavir oral powder 100 mg to the core list of the EML and EMLc for the treatment of HIV infection, in line with recommendations in current WHO guidelines, noting the importance of the availability of quality, age-appropriate paediatric dosage forms of antiretroviral medicines.

Lopinavir + ritonavir – new formulation – EML and EMLc (ATC Code J05AR10)

NEW FORMULATION: The Expert Committtee recommended the addition of a new formulation of lopinavir + ritonavir (LPV/r) oral granules 40 mg + 10 mg fixed-dose combination to the core list of the EMLc for the treatment of children with HIV infection, in line with recommendations in current WHO guidelines, noting the importance of the availability of quality, age-appropriate paediatric dosage forms of antiretroviral medicines.

The Committee recommended the new LPV/r oral granules and the existing LPV/r capsules containing oral pellets should be listed collectively as "solid oral dosage form", for consistency with the 2018 optimal pediatric ARV formulary.

Dolutegravir – addition – EMLc (ATC Code J05AX12)

ADDITION: The Expert Committee recommended the addition of dolutegravir 50 mg tablets to the core list of the EMLc for treatment of HIV infection in paediatric patients weighing 25kg or more, in combination with an optimized NRTI backbone regimen, in line with recommendations in current WHO Guidelines.

The Committee acknowledged the important need to expand HIV treatment options for children. The Committee noted the available evidence for use of dolutegravir in children was largely limited to pharmacokinetic and safety data from two ongoing paediatric trials but considered that extrapolation of efficacy from adult trials was acceptable.

Raltegravir – new formulation – EML and EMLc (ATC Code J05AX08)

ADDITION: The Expert Committee recommended the addition of a new formulation of raltegravir granules for oral suspension 100 mg to the core list of the EML and EMLc for the treatment of HIV infection in line with recommendations in current WHO guidelines. The Committee considered that this formulation of raltegravir could facilitate treatment of neonates and paediatric patients and would be a suitable alternative for adult and paediatric patients for whom dolutegravir is not available or is not tolerated.

Dolutegravir + lamivudine + tenofovir disoproxil fumarate – addition – EML (ATC Code to be assigned)

ADDITION: The Expert Committee recommended the addition of the fixed-dose combination formulation of dolutegravir + lamivudine + tenofovir disoproxil fumarate to the core list of the EML

for treatment of HIV infection in adults and adolescents. The Committee noted the demonstrated efficacy and safety of DTG-based regimens in treatment-naïve patients, and that DTG-based regimens are now recommended as preferred first-line therapy in WHO Guidelines for adults and adolescents initiating antiretroviral treatment.

The Committee also considered that the availability of fixed-dose combinations of antiretroviral therapies provides benefits to patients in terms of ease of administration and reduced pill burden, which can contribute to improved therapeutic adherence.

6.4.4.2: Medicines for hepatitis C

6.4.4.2.1: Pangenotypic direct-acting antiviral combinations

Glecaprevir + pibrentasvir – addition – EML (ATC Code J05AP57)

ADDITION: The Expert Committee recommended the addition of the fixed-dose combination of glecaprevir + pibrentasvir to the core list of the EML for the treatment of adult patients with chronic hepatitis C virus infection, based on evidence of pan-genotypic effectiveness and an acceptable safety profile. The Committee noted that this combination is one of three pan-genotypic combinations recommended in the current WHO guidelines for treatment of hepatitis C and is suitable for use in patients with or without compensated cirrhosis.

The Committee noted that the manufacturer and the Medicines Patent Pool (MPP) have entered into licensing agreement for this product to accelerate access in 99 LMICs. However, the Committee noted with concern that some LMICs with a high burden of hepatitis C are not included in this agreement and encouraged the manufacturer and the MPP to address this issue to ensure patients in these high-burden countries have equitable access.

The Committee recommended that the hepatitis C medicines section of the Model List be amended to differentiate between pangenotypic (glecaprevir + pibrentasvir, sofosbuvir + daclatasvir and sofosbuvir + velpatasvir), non-pangenotypic direct acting antivirals, and other antivirals for hepatitis C. The pangenotypic regimens should be considered as therapeutically equivalent to facilitate selection and procurement by countries at national level.

DELETION: The Expert Committee then considered whether it was appropriate to delete non-pangenotypic treatments for hepatitis C, and recommended the deletion of simeprevir, whose place in therapy was now superseded by the pan-genotypic options. The Committee recommended that other non-pangenotypic treatments could be considered for deletion from the EML in the future.

6.5.3: Antimalarial medicines

6.5.3.2 For chemoprevention

Sulfadoxine + pyrimethamine – new indication IPTi – EMLc (ATC Code P01BD51)

NEW INDICATION: The Expert Committee recommended listing of sulfadoxine + pyrimethamine 250 mg + 12.5 mg fixed-dose combination tablet on the core list of the EMLc for the new indication of intermittent preventive treatment (of malaria) in infancy (IPTi) on the basis of demonstrated efficacy and acceptable safety, and in alignment with WHO malaria guideline recommendations.

The Expert Committee noted the lack of evidence of the impact of the use of SP-IPTi on antimicrobial resistance and encouraged further assessment and monitoring in this regard within programme delivery.

Sulfadoxine + pyrimethamine – new indication IPTp – EML (ATC Code P01BD51)

NEW INDICATION: The Expert Committee recommended the listing of sulfadoxine + pyrimethamine 500 mg + 25 mg fixed-dose combination tablet on the core list of the EML for the new indication of intermittent preventive treatment of malaria in pregnancy (IPTp) on the basis of demonstrated efficacy in terms of improved outcomes for mothers and newborns, and acceptable safety, and in alignment with WHO malaria guideline recommendations.

The Expert Committee noted the lack of evidence of the impact of the use of SP-IPTp on antimicrobial resistance and encouraged further assessment and monitoring in this regard within programme delivery.

Amodiaquine with sulfadoxine + pyrimethamine – addition – EMLc (ATC Codes P01BA06, P01BD51)

ADDITION: The Expert Committee recommends the addition of co-packaged amodiaquine with sulfadoxine + pyrimethamine to the core list of the EMLc for seasonal malaria chemoprevention in children on the basis of acceptable safety and demonstrated benefits for reducing clinical malaria episodes and serious malaria episodes and reduced rates of mortality and anaemia, and in alignment with WHO malaria guideline recommendations.

The Expert Committee noted the lack of evidence of the impact of the use of amodiaquine with sulfadoxine + pyrimethamine for SMC on antimicrobial resistance and encouraged further assessment and monitoring in this regard within programme delivery.

6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

Fexinidazole – addition – EML and EMLc (ATC Code P01CA03)

ADDITION: The Expert Committee recommended the listing of fexinidazole on the core list of the EML and EMLc for treatment of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

The Committee noted that fexinidazole was demonstrated in clinical trials to have success rates within acceptable margins compared to NECT, and acceptable safety. The Committee acknowledged that as an orally administered treatment, use of fexinidazole may offer both patient and health-system advantages compared to parenteral administration of other medicines for this disease.

The Committee noted that fexinidazole would be provided free of charge through the WHO NTD department to National Sleeping Sickness Control Programmes and treatment centres and could contribute to the goal of disease eradication, particularly in areas where access to health facilities is limited.

6.6 Medicines for ectoparasitic infections

Ivermectin – new indication scabies – EML and EMLc (ATC Code P02CF01)

NEW INDICATION: The Expert Committee recommended listing of ivermectin on the core list of the EML and EMLc for the new indication of treatment of scabies. The Committee noted that oral ivermectin treatment is associated with comparable effectiveness to topical therapies and has acceptable safety. The Committee also noted the effectiveness of ivermectin as a public health intervention when delivered via mass drug administration programmes.

The Committee considered that the ease of oral administration compared to topical administration may also represent an advantage for patients in terms of compliance.

Section 7: ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

Sumatriptan – <u>rejected</u> application for acute migraine – EML (ATC Code N02CC01)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of sumatriptan to the core list of the EML for the treatment of adult patients with acute migraine.

The Committee noted that the available evidence supported the superior effectiveness of sumatriptan compared to placebo, but that evidence comparing sumatriptan with currently listed analgesics (aspirin and paracetamol) showed varying results, including no difference in effect.

However, the Committee also noted that sumatriptan is recommended as first-line therapy for migraine in many international guidelines and would welcome a future review of additional data of the role of sumatriptan in the context of other migraine therapies.

Section 8: IMMUNOMODULATORS AND ANTINEOPLASTICS

8.1 Immunomodulators for non-malignant disease

Medicines for multiple sclerosis – rejected application – EML and EMLc

Glatiramer acetate (ATC Code L03AX13)
Fingolimod (ATC Code L04AA27)
Ocrelizumab (ATC Code L04AA36)

REJECTED APPLICATION: The Expert Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments and noted the large number of supporting letters that were received in relation to the application.

The Committee appreciated the approach taken in the application to propose a limited number of essential medicines for MS but noted that the superiority of the presented medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge.

The Committee noted that some commonly used treatments were not included (e.g. azathioprine, natalizumab, dimethyl fumarate, cladrabine) or were not given full consideration (rituximab) and the reasons for their exclusion were not clear. The Committee also noted ongoing development in international MS guidelines and would welcome a revised application for EML inclusion in the future which considers the relative roles of all available medicines for MS.

In particular, the Committee noted the evidence presented in the application in relation to rituximab. The Committee agreed that rituximab could have a relevant clinical role in treatment of MS and recommended that any future application should include evidence for rituximab versus active comparators, not just placebo.

The Committee, therefore did not recommend the addition of glatiramer acetate, fingolimod and ocrelizumab to the Model Lists at this time, and would welcome a revised application which comprehensively reviews the relative roles of relevant available medicines for MS.

TNF-alfa inhibitors for chronic inflammatory diseases – addition – EML and EMLc

Etanercept (ATC Code L04AB01)
Infliximab (ATC Code L04AB02)
Adalimumab (ATC Code L04AB04)
Certolizumab pegol (ATC Code L04AB05)
Golimumab (ATC Code L04AB06)

ADDITION: The Committee recognized that these auto-immune disorders are highly debilitating and that there is a public health need for effective treatments for patients who do not respond adequately to first-line treatments (e.g. methotrexate).

The Expert Committee recommended the addition of adalimumab with a square box to the complementary list of the EML and EMLc for the second-line treatment of severe chronic inflammatory autoimmune disorders (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease) on the basis of the positive benefit to harm profile of these medicines.

For adult patients, therapeutically equivalent alternatives to adalimumab are limited to etanercept, infliximab, certolizumab pegol and golimumab. For children, therapeutically equivalent alternatives should be limited to etanercept and infliximab.

The Committee also recognized that these medicines are associated with a significant budget impact to health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to more market competition. The Committee recognized a potential expansion of the role of the Medicines Patent Pool to biological medicines such as these as an opportunity to facilitate affordable access. Quality-assured available biosimilars of these medicines should also be considered as therapeutically equivalent for procurement purposes.

The Expert Committee recommended that WHO take action to facilitate access to these medicines through the WHO pre-qualification programme, and through collaboration with partners such as the Medicines Patent Pool.

8.2 Antineoplastics and supportive medicines

Cancer medicines for children

New medicines to be added to the EMLc – extending adult indications to children	
Medicine	**Paediatric indication(s)**
All-trans retinoic acid (ATRA)	Acute promyelocytic leukaemia
Dasatinib	Imatinib-resistant chronic myeloid leukaemia
Fluorouracil	Nasopharyngeal carcinoma Early-stage colon cancer Early-stage rectal cancer Metastatic colorectal cancer
Enoxaparin (*with a square box*)	For use as anticoagulant
Hydroxycarbamide	Chronic myeloid leukaemia
Imatinib	Chronic myeloid leukaemia Gastrointestinal stromal tumour
Irinotecan	Metastatic colorectal cancer
Nilotinib	Imatinib-resistant chronic myeloid leukaemia
Oxaliplatin	Early stage colon cancer Metastatic colorectal cancer
Procarbazine	Hodgkin lymphoma
Rituximab	Diffuse large B-cell lymphoma
REJECTED Zoledronic acid	Malignancy-related bone disease
Extension of indications for currently listed medicines	
Medicine	**Indication**

Bleomycin	Kaposi sarcoma
Doxorubicin	Kaposi sarcoma
Vincristine	Kaposi sarcoma
Cisplatin	Nasopharyngeal cancer
Cyclophosphamide	Diffuse large B-cell lymphoma
Prednisolone	Diffuse large B-cell lymphoma
Cytarabine	Acute promyelocytic leukaemia
Daunorubicin	Acute promyelocytic leukaemia
Mercaptopurine	Acute promyelocytic leukaemia
Methotrexate	Acute promyelocytic leukaemia
Cytarabine	Acute myelogenous leukaemia
Hydroxycarbamide	Chronic myeloid leukemia

ADDITION: The Expert Committee recommended the addition to the complementary list of the EMLc of ATRA, dasatinib, fluorouracil, imatinib, irinotecan, nilotinib, oxaliplatin, procarbazine and rituximab for the paediatric cancer indications outlined in the table.

NEW INDICATION: The Committee also recommended the extension of the current listings on the EMLc of bleomycin, doxorubicin, vincristine, cisplatin, cyclophosphamide, prednisolone, cytarabine, daunorubicin, mercaptopurine, methotrexate, cytarabine and hydroxycarbamide to include the indications outlined in the table.

ADDITION: The Committee also recommended the addition to the core list of the EMLc of enoxaparin *with a square box* for use as an anticoagulant in children.

REJECTED APPLICATION: The Expert Committee did not recommend the addition of zoledronic acid to the complementary list of the EMLc for the treatment of malignancy-related bone disease. The Committee noted that data for its use in children are scant and fragmented. The Committee was also concerned that the effects of zoledronic acid in some paediatric cancers (e.g. osteosarcoma) were largely negative, and that there are insufficient long-term safety data of bisphosphonate use in paediatric cancer patients to be reassured of an acceptable benefit to harm ratio.

Furthermore, the Committee noted that although use of bisphosphonates in paediatric patients has been reported to be well tolerated, the impact of use in the context of patients with actively growing skeleton is not yet fully known.

Medicines for children with cancer – text clarifications

The application requested amendments to the text of the listings for a number of medicines and cancer indications on the EMLc:

1. Include alternate common names for some currently listed cancer medicines;
2. Include alternate common names for some listed indications;
3. Revised diagnosis terminology for germ cell tumours;
4. Alignment and addition of formulations;
5. Inclusion of variant formulations of listed medicines;
6. Addition of usage and supportive indications.

Following consideration of the proposals in the application, the Expert Committee made the following recommendations:

1. The additional alternate common names for medicines should not be added to the Model Lists. The current listings refer to the international non-proprietary names (INN) of the medicines. INN is the preferred nomenclature for medicines on the Model Lists.

2. The indication terminology for acute myelogenous leukaemia and Wilms tumour should be amended as proposed, as this would be consistent with ICD-11 terminology for these indications.
3. The indication of "malignant germ cell tumour" should not replace the indications of ovarian and testicular germ cell tumour as the Committee has not reviewed evidence for use of the relevant medicines in the treatment of germ cell tumours other than ovarian and testicular. Extending the indication to all germ cell tumours would require a full application.
4. With regard to formulation amendments, the Committee recommended that formulations of dexamethasone should be consistently listed across different sections of the list. The Committee also recommended that proposed new strengths of existing dose forms of calcium folinate, cyclophosphamide, etoposide should be added. However, the Committee did not recommend listing of the new dose forms for these medicines, and for mercaptopurine and methotrexate.
5. The Committee did not recommend the separate listing of prednisone with prednisolone, noting that the square box listing of prednisolone should be interpreted as including prednisone as an alternative. The Committee did not recommend the listing of etoposide phosphate as a variant of etoposide, as it considered that a full application would be appropriate to consider the clinical place of this medicine as an alternative to etoposide. The Committee also did not recommend listing for topical lidocaine + prilocaine, again considering that a full application would be required for this new combination product.
6. The Committee recommended including the indication "tumour lysis syndrome" with the listing for allopurinol. The Committee did not recommend including the other proposed supportive care indications with the listings of calcium folinate and mesna. Nor did the Committee recommend the proposed cautionary text for methotrexate and vincristine. The Committee acknowledged the critical importance of these messages but considered that this text was better suited for clinical practice guidelines, medication safety information and product packaging than on the Model Lists. The Committee did not recommend the proposed cautionary text about codeine with the listing for morphine. The Committee noted that codeine is not listed on the EMLc, and that alternatives to morphine are specified in the current listing as being limited to hydromorphone and oxycodone.

8.2.1 Cytotoxic medicines

Arsenic therapies – addition – EML and EMLc

Arsenic trioxide (ATC Code L01XX27) Realgar-Indigo naturalis formula (RIF) (ATC Code: N/A)
The Committee endorsed the recommendations of the Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration arsenic-containing regimens for APML. **ADDITION:** The Expert Committee recommended the addition of arsenic therapies (intravenous arsenic trioxide and oral realgar-Indigo naturalis formulation) to the complementary list of the EML and EMLc for use in combination with all-trans-retinoic acid (ATRA) for treatment of patients with acute promyelocytic leukaemia, both newly diagnosed and relapsed.

ADDITION AND EXTENDED LISTINGS: In consideration of a separate application of cancer medicines for children, the Committee also recommended the addition of ATRA to the EMLc, and extending the listings on the EMLc of cytarabine, daunorubicin, mercaptopurine, and methotrexate to include APML.

The Committee noted that treatment with ATRA plus arsenic was associated with high response rates and significant improvements in event-free and overall survival compared to ATRA plus chemotherapy and has a more favourable toxicity profile.

Medicines for cervical cancer – new indication – EML

Cisplatin (ATC Code L01XA01)
Carboplatin (ATC Code L01XA02)
Paclitaxel (ATC Code L01CD01)
REJECTED Fluorouracil (ATC Code L01BC02)

EXTENDED LISTINGS: The Expert Committee recommended extending the indications for cisplatin, carboplatin and paclitaxel on the complementary list of the EML to include treatment of invasive cervical cancer. The Committee considered that the evidence presented demonstrated these medicines to be associated with relevant survival benefits for patients. The Committee noted that regimens including these medicines are considered standard care in the curative and non-curative settings for cervical cancer.

Cisplatin is currently listed for use in the curative setting as a radiosensitizer and its listing is recommended to be extended to include the non-curative setting. Carboplatin is recommended for listing both in the curative and non-curative settings, and paclitaxel is recommended for listing in the non-curative setting.

REJECTED APPLICATION: The Expert Committee did not recommend extending the indications for fluorouracil to include treatment of cervical cancer in the curative setting. The Committee noted that when combined with radiotherapy, fluorouracil alone or in combination with cisplatin, was not associated with additional benefit compared to radiotherapy alone or cisplatin plus radiotherapy.

Pegaspargase – addition – EML and EMLc (ATC Code L01XX24)

ADDITION: The Expert Committee recommended the addition of pegaspargase to the complementary list of the EML and EMLc for use in the treatment of acute lymphoblastic leukaemia. The listing should indicate that quality-assured biosimilars of pegaspargase should also be considered as essential.

The Committee noted pegaspargase was associated with less immunogenicity and development of neutralizing antibodies than native asparaginase, which may offer advantages in terms of improved patient adherence enabling completion of treatment, thereby reducing the risk of relapse.

8.2.2 Targeted therapies

Pertuzumab – rejected application – EML (ATC Code L01XC13)

REJECTED APPLICATION: The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of pertuzumab.

The Committee acknowledged that pertuzumab was associated with a relevant survival benefit, well beyond the established threshold, as first-line treatment of metastatic breast cancer, based on the results reported in the CLEOPATRA trial. However, the Committee expressed reservations about the generalizability of CLEOPATRA results in metastatic breast cancer and consistency of the clinical effectiveness of pertuzumab among studies both in early and metastatic breast cancer. These reservations are expanded below.

The Committee noted that only approximately 10% of patients in CLEOPATRA had received trastuzumab in the adjuvant or neoadjuvant setting. The Committee was concerned that the observed survival gains may not therefore be generalizable to patients with metastatic disease who have received prior adjuvant or neoadjuvant trastuzumab, making the magnitude of benefit in this population sub-group uncertain. The Committee also noted the results reported in the MARIANNE trial, where pertuzumab in combination with T-DM1 was not shown to have greater clinical benefit compared to trastuzumab plus chemotherapy or T-DM1 alone. The Committee was unable to reconcile the differences in the outcomes reported in the MARIANNE and CLEOPATRA trials.

The Committee also noted that the relevant survival gains observed in CLEOPATRA for metastatic breast cancer were not replicated in trials of pertuzumab in early stage breast cancer. The Committee accepted that trial results suggest pertuzumab offers a small incremental overall and disease-free survival benefit compared to placebo, based on an analysis at around 3 years median follow-up. The Committee considered that continued follow up was important to assess long-term overall survival but thought it unlikely that the magnitude of benefit would be greater with longer follow-up, given that anti-HER2 treatments are typically associated with a reduction in early recurrences, followed by a plateau effect.

The Expert Committee therefore did not recommend the addition of pertuzumab to the complementary list of the Model List for the treatment of early stage and metastatic HER-2 positive breast cancer. The Committee considered that the available evidence did not demonstrate a clinically meaningful survival benefit in early stage disease, and that there was important uncertainty surrounding the estimated magnitude of survival benefit in metastatic disease, with results seen in CLEOPATRA not replicated in other trials.

It was Committee's view that questions associated with differences in results from the CLEOPATRA and MARIANNE trials should be resolved by integration of the raw, individual patient trial data and independent re-analysis following a set of pre-planned hypotheses. The Committee recommended that WHO considers requesting access to the raw clinical trial data from CLEOPATRA and MARIANNE from the applicant, for an independent re-analysis arranged by WHO, and present the report of any such independent re-analysis, to the 2021 Expert Committee for consideration.

Rituximab – rejected application for new formulation – EML (ATC Code L01XC02)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of new sub-cutaneous injection formulations of rituximab to the complementary list of the EML for use in the treatment of diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma.

The Expert Committee acknowledged the potential benefits of the sub-cutaneous formulation over the listed intravenous formulation. However, with the availability of biosimilar versions of intravenous rituximab, the Committee was concerned that listing of the sub-cutaneous formulation, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

To help improve access, the Expert Committee recommended the current listing for intravenous rituximab on the EML should indicate that quality-assured biosimilars of rituximab should also be considered as essential medicines. In addition, the Expert Committee recommended that WHO continue to facilitate access to biosimilars through the Prequalification programme and WHO Collaborative Registration Procedure.

Trastuzumab – rejected application for new formulation – EML (ATC Code L01XC03)

REJECTED APPLICATION: The Committee did not recommend the addition of new sub-cutaneous injection formulations of trastuzumab to the complementary list of the EML for use in the treatment of early stage and metastatic HER-2 positive breast cancer.

The Expert Committee acknowledged the potential benefits of the sub-cutaneous formulation over the listed intravenous formulation. However, with the availability of biosimilar versions of intravenous trastuzumab, the Committee was concerned that listing of the sub-cutaneous formulation, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

To help improve access, the Expert Committee recommended the current listing for intravenous trastuzumab on the EML should indicate that quality-assured biosimilars of trastuzumab can also be considered as essential medicines. In addition, the Expert Committee recommended that WHO continue to facilitate access to biosimilars through the Prequalification programme and WHO Collaborative Registration Procedure.

Trastuzumab emtansine (T-DM1) – rejected application for addition – EML (ATC Code L01XC14)

REJECTED APPLICATION: The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of trastuzumab emtansine. The Committee acknowledged that for second line treatment of metastatic breast cancer, trastuzumab emtansine was associated with a relevant survival benefit, within the range of the established threshold. However, the Committee noted that survival benefits did not meet the four to six month threshold when trastuzumab emtansine was used as first line treatment in the metastatic setting, or in early stage breast cancer.

Existing EML-listed options are available for metastatic disease and may be suitable alternatives (e.g., trastuzumab, taxanes, etc.). However, the Committee noted the current challenges in achieving full access to trastuzumab in many settings. Taking this into account, trastuzumab emtansine for second-line treatment of metastatic disease (i.e. late in the care pathway) was considered to be a lower priority for EML inclusion at this time.

Compared to the 2017 application, the Committee noted that few new clinical data were included in the current application and that the request was not based on a comprehensive review encompassing additional breast cancer medicines, compared with the standard of care, which would allow countries to understand the additional value of adding each option to national EMLs.

The Expert Committee therefore did not recommend the addition of trastuzumab emtansine to the complementary list of the EML for the treatment of unresectable locally advanced and metastatic HER2-positive breast cancer.

Tyrosine-kinase inhibitors for non-small cell lung cancer – addition – EML

Afatinib (ATC Code L01XE13) Erlotinib (ATC Code: L01XE03) Gefitinib (ATC Code: L01XE02)
ADDITION: The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of the tyrosine kinase inhibitors afatinib, erlotinib and gefitinib. The Committee noted that afatinib, erlotinib and gefitinib were all scored as 4/5 on the ESMO-MCBS v1.1 for this indication. The Expert Committee recommended the addition of erlotinib with a square box to the complementary list of the EML for first-line treatment of EGFR mutation positive advanced non-small cell lung cancer. Afatinib and gefitinib should be considered as therapeutically equivalent alternatives. The Committee noted that these medicines are associated with relevant survival benefits for patients, acceptable toxicity and improvements in quality of life compared to chemotherapy. The Committee also noted that since these medicines were considered for inclusion on the EML in 2015, generic versions of these medicines are more widely available, as are quality-assured diagnostic molecular tests for EGFR mutations.

8.2.2 Targeted therapies (bortezomib)

8.2.3 Immunomodulators (lenalidomide, thalidomide)

Medicines for multiple myeloma – addition – EML

Bortezomib (ATC Code L01XX32) Lenalidomide (ATC Code L01AX04) Thalidomide (ATC Code L04AX02)

The Committee acknowledged the treatment of MM to be complex and recognized the need to provide the best available care within the context of both non-transplant and transplant settings.

ADDITION: The Expert Committee recommended the addition of bortezomib, lenalidomide and thalidomide to the complementary list of the EML for the treatment of multiple myeloma patients in both non-transplant and transplant eligible/available settings, on the basis of good evidence showing large improvement in survival outcomes with acceptable safety for patients with newly-diagnosed multiple myeloma.

With regard to MM treatment in transplant-eligible populations, the Committee noted the additional evidence presented as part of the review process supporting standard regimens used in the induction phase before ASCT involving three-drug combinations: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone) and RVD (lenalidomide, bortezomib, dexamethasone); and of the benefit of lenalidomide maintenance therapy following ASCT.

ADDITION and ADDITIONAL INDICATION: In the non-transplant setting, the Committee acknowledged that the proposed medicines are administered as part of treatment regimens involving companion cytotoxic agents and/or steroids (melphalan, cyclophosphamide, prednisone, dexamethasone). Accordingly, the Committee recommended the addition of melphalan to the complementary list of the EML for treatment of multiple myeloma, and that the current listings for cyclophosphamide, doxorubicin, prednisone and dexamethasone be extended to include multiple myeloma as an indication.

8.2.3 Immunomodulators

Anti PD-1 / PD-L1 Immune checkpoint inhibitors – application for addition – EML and EMLc

Atezolizumab (ATC Code L01XC32) Nivolumab (ATC Code L01XC17) Pembrolizumab (ATC Code L01XC18)
The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of the immune checkpoint inhibitors. **ADDITION:** The Committee noted that there were no treatment options for metastatic melanoma currently included on the Model List. The Committee recommended the addition of nivolumab and pembrolizumab to the complementary list of the EML, for use as front-line monotherapy for treatment of patients with unresectable and metastatic melanoma on the basis of evidence of significantly increased overall survival for patients that met the recommended threshold for benefit, and in the absence of other EML-listed treatment options. Listing should be for nivolumab with a square box indicating pembrolizumab as a therapeutically equivalent alternative. The Committee noted that nivolumab was scored as 4/5 on the ESMO-MCBS v1.1 for this indication. The Committee considered that more mature data would be necessary before listing of these medicines could be considered for use in adjuvant indications of radically resected melanoma.

REJECTED APPLICATION: The Committee did not recommend listing of atezolizumab, nivolumab or pembrolizumab for treatment of patients with metastatic NSCLC at this time, as the Committee considered that their precise place in the treatment/immunotherapy of this condition is still evolving. The Committee noted the evidence of efficacy in the treatment of patients with metastatic NSCLC with these agents. The Committee observed that the duration of follow-up of the single studies for frontline and second line immunotherapy in trials for lung cancer was generally shorter than three years and considered that data from longer follow-up would better capture the actual magnitude of benefit. By the time of the next Expert Committee meeting in 2021, more mature data will be available for metastatic NSCLC and also for use of these agents in locally advanced non-resectable disease, and as adjuvant therapy.

Furthermore, the Committee noted that the landscape of clinical development of cancer immunotherapy still has some areas of uncertainty with regard to the optimal time for introduction of treatment (front-line or second line), appropriate patient selection, and whether or not use of ICIs in combination with other medicines is superior.

The Expert Committee expressed concern about the potential budget impact of oncology medicines which could be an impediment to access, and countries may not be able to list these medicines on their national EMLs. Therefore, the Committee recommended that WHO engage stakeholders to find ways to facilitate better access and affordability as a high priority through avenues such as the Medicines Patent Pool, WHO prequalification and collaborative registration procedures. The Committee also recommended ongoing activities of the EML Cancer Medicines Working Group to include identification of obstacles to access and affordability of cancer medicines, and pricing data collection.

8.2.4 Hormones and antihormones

Medicines for prostate cancer – EML

Abiraterone (ATC Code: L02BX03) Enzalutamide (ATC Code: L02BB04)
The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of abiraterone and enzalutamide. **ADDITION**: The Expert Committee recommended the addition of abiraterone to the complementary list of the EML for use in the treatment of metastatic castration-resistant prostate cancer. The Expert Committee acknowledged the significant public health burden of prostate cancer, which afflicts an increasing number of people in all countries, irrespective of income. The Committee recalled that the EML currently includes docetaxel, bicalutamide and leuprorelin for use in the treatment of metastatic prostate cancer. However, a significant proportion of patients will not respond to these medicines and patients will ultimately develop resistance. The Committee noted that abiraterone and enzalutamide have each been shown to be effective treatments for metastatic castration-resistant prostate cancer, both in chemotherapy-naive and in pre-treated patients. The Committee noted that abiraterone had not shown any relevant clinical

advantage over enzalutamide in terms of efficacy outcomes or safety. However, the Committee recognized the potential advantages offered by abiraterone in terms of emerging dosing strategies (lower doses may be possible when administered with food), reduced pill burden potentially improving adherence, wider availability of generics and potential associated cost savings.

REJECTED APPLICATION: Given that metastatic prostate cancer often requires treatment over longer periods of time (above 1 year) and that low dosing and availability of generics would be associated with substantial cost savings, the Committee decided not to recommend listing abiraterone with a square box indicating enzalutamide as an alternative. While enzalutamide remains an effective therapeutic option for mCRPC, its use instead of abiraterone could result in considerable additional expenditure at country level, without additional clinical benefit. The Committee considered that addition of abiraterone alone on the EML serves to support its use, promoting competition between brand and generic medicines, and improving access and affordability.

Section 10: MEDICINES AFFECTING THE BLOOD

10.2 Medicines affecting coagulation

Direct oral anticoagulants (DOACs) - dabigatran, rivaroxaban, apixaban, edoxaban – addition - EML

Direct oral anticoagulants

Apixaban (ATC Code B01AF02)
Dabigatran etexilate (ATC Code B01AE07)
Edoxaban (ATC Code B01AF03)
Rivaroxaban (ATC Code B01AF01)

ADDITION: The Committee recommended the addition of dabigatran with a square box to the core list of the EML for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for treatment of venous thromboembolism based on favourable efficacy and acceptable safety. The square box refers to apixaban, edoxaban and rivaroxaban as therapeutically equivalent alternatives.

The Committee noted that the DOACs demonstrated clinical benefits in terms of reduced mortality, reduced risk of stroke or systemic embolism, and were associated with fewer severe/major bleeding episodes compared to well controlled warfarin in patients with NVAF.

In the treatment of patients with VTE, DOACs were associated with small reductions in mortality, risk of subsequent / recurrent thromboembolic events and major bleeding compared to low-molecular weight heparin and vitamin K antagonists.

The use of DOACs may also have relevant health system benefits related to the infrastructure required for warfarin treatment monitoring, as they do not require laboratory monitoring. The Committee noted that DOACs have higher daily treatment costs than warfarin but have been found to be a cost-effective intervention. It is recommended that countries take all these factors into consideration when selecting anticoagulants to best suit their national and local needs and circumstances.

The Committee recommended that WHO take action to facilitate access to these medicines through the WHO prequalification programme, and through collaboration with partners such as the Medicines Patent Pool.

Section 12: CARDIOVASCULAR MEDICINES

12.3 Antihypertensive medicines

Fixed-dose combination antihypertensives - addition – EML

Lisinopril + amlodipine (ATC Code C09BB03)
Lisinopril + hydrochlorothiazide (ATC Code C09BA03)
Telmisartan + amlodipine (ATC Code C09DB04)
Telmisartan + hydrochlorothiazide (ATC Code C09DA07)

ADDITION: The Committee recommended the addition of four two-drug FDCs, each with multiple strength formulations to the core list of the EML for use in the treatment of hypertension. Each component of the combinations should be listed with a square box, indicating that other medicines within the respective pharmacological classes represent therapeutically equivalent alternatives. For the calcium channel blocker component, the square box should be limited to dihydropyridine class of calcium channel blockers.

The Committee accepted the efficacy of FDC antihypertensives compared to placebo or monotherapy for reducing blood pressure and cardiovascular events but expressed concern that the application did not provide strong evidence of the claimed advantages of FDC therapy versus dual component monotherapy. However, the Committee accepted that many patients require multiple antihypertensive treatment to achieve blood pressure targets and recognized that FDCs may confer advantages for patients over single medicines given concomitantly in terms of better adherence and reduced pill burden.

The Committee considered that the ongoing availability of single agent antihypertensive medicines is critical to allow treatment modification where necessary, and that FDCs should not displace single components at country level.

The Committee also noted that the availability of multiple FDCs in varying strengths may be associated with significant supply chain and affordability issues for LMICs. The Committee noted that the cost of FDCs versus the sum of the cost of component monotherapies varies in different settings and is not always the same (or lower) than the sum of component monotherapies. The Committee stressed that the cost of FDCs should not be significantly higher than the sum of the cost of their component monotherapies. In particular, in resource-constrained settings where access is limited, the opportunity costs associated with treating patients with FDCs must be considered.

12.5 Antithrombotic medicines

12.5.2 Thrombolytic medicines

Alteplase - addition – EML (ATC Code B01AD02)

ADDITION: The Committee recommended the addition of alteplase to the complementary list of the EML as a thrombolytic agent for use in patients diagnosed with acute ischaemic stroke on the basis of the evidence presented of improved patient outcomes in terms of reduced death or dependence when alteplase is administered within 4.5 hours of the onset of stroke symptoms.

The Committee acknowledged the significant global burden of stroke in terms of death and disability, and particularly in low- and middle-income countries. The Committee noted that optimal use of alteplase would require timely and highly organized care pathways, in facilities that are equipped and capable of managing stroke patients.

Section 17: GASTROINTESTINAL MEDICINES

17.2 Antiemetic medicines

Aprepitant – addition – EML and EMLc (ATC Code A04AD12)

ADDITION: The Committee recognized the importance of adequate control of nausea and vomiting in patients undergoing cancer chemotherapy, in terms quality of life and clinical outcomes of treatment.

The Expert Committee recommended the addition of aprepitant to the complementary list of the EML and EMLc as an antiemetic medicine for the supportive care of cancer patients receiving moderately to highly emetogenic chemotherapy on the basis of a favourable benefit to risk profile.

The Committee noted that aprepitant, in combination with dexamethasone and a 5HT3 receptor antagonist (e.g. ondansetron), is more effective than standard antiemetic therapy at reducing both acute and delayed onset nausea and vomiting associated with chemotherapy.

Ondansetron – square box – EML and EMLc (ATC Code A04AA01)

ADDITION: The Expert Committee recommended the addition of a square box to the listing of ondansetron on the EML and EMLc, noting that the original recommendation to list ondansetron in 2009 had included a square box.

17.5 Medicines used in diarrhoea

Oral rehydration salts (ORS) and zinc (co-packaged) – new formulation – EMLc (ATC Codes A07CA, A12CB01)

ADDITION: The Committee recommended the inclusion of co-packaged oral rehydration salts (ORS) and zinc sulfate tablets on the core list of the EMLc. The Committee considered that since these products are recommended to be administered together in the management of diarrhoea, the availability of the co-packaged product will be practical and support better adherence to treatment. Countries may also realize cost savings with the co-packaged product.

Section 18: MEDICINES FOR ENDOCRINE DISORDERS

18.5 Insulin and other medicines used for diabetes

Long-acting insulin analogues (including biosimilars) – <u>rejected</u> application for addition – EML

Long-acting insulin analogues (including biosimilars)

Insulin detemir (ATC Code A10AE05)
Insulin glargine (ATC Code A10AE04)
Insulin degludec (ATC Code A10AE06)

REJECTED APPLICATION: The Committee acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin remains a public health challenge in many countries.

The Committee did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Expert Committee, that while long-acting insulin analogues are an effective treatment for type 1 diabetes, the available evidence shows efficacy and safety advantages of analogues compared to human insulin which are insufficiently large to justify the cost differential that continues to exist in most settings.

The Committee remained concerned about the ongoing problems of access and affordability of insulin worldwide, despite human insulin not being patented. The Committee noted the long-standing domination of the insulin market by three manufacturers, limiting broader competition and slowing the entry of biosimilars to the market.

Recognizing the complexities of these problems and the need for a wider understanding of the insulin market and access to insulin, the Committee recommended WHO coordinate a series of actions to address the issues of insulin access and affordability. In the absence of other coordinated actions, the

Committee considered that the inclusion of insulin analogues for adults on the EML would be inadequate to address the underlying issues of poor access and affordability of insulins more generally.

The Committee recommended that a WHO-led approach should be multi-factorial and multi-disciplinary and should include:

- establishment of an independent WHO technical working group on access to insulin;
- consultation with Member States and other stakeholders to identify/clarify barriers to access at country level;
- strategies to address current regulatory barriers for biosimilar insulins, such as the expansion of the WHO Prequalification Programme;
- development of a comprehensive approach to address insulin prices, including mechanisms for pooled procurement;
- identification of evidence and research gaps regarding insulin use and supply, including setting-specific differences in clinical practice and health systems (e.g. food insecurity, displaced populations, emergencies).

The Committee would welcome a report that comprehensively describes the actions that are undertaken by WHO over the next biennium and an application that reviews more in depth current challenges for optimal global access and the role of insulin analogues in children.

18.6 Medicines for hypoglycaemia

Diazoxide – addition- EMLc (ATC Code V03AH01)

ADDITION: The Committee recommended the addition of diazoxide to the complementary list of the EMLc for the management of hypoglycaemia secondary to prolonged hyperinsulinism (HI), based on evidence of favourable efficacy and tolerability, and taking into account the serious consequences of this condition in children not treated.

The Committee noted the variable global availability and reliability of supply of diazoxide and considered inclusion of diazoxide on the EMLc could help to facilitate more reliable access.

18.7 Thyroid hormones and antithyroid medicines

Medicines for first-line treatment of primary hyperthyroidism – review – EML and EMLc

Methimazole (ATC Code H03BB01) Propylthiouracil (ATC Code H03BA02)
The Committee recommended the addition of methimazole with a square box to the core list of the EML and to the complementary list of the EMLc for use as first-line therapy for hyperthyroidism. The square box listing should specify carbimazole as a therapeutically equivalent alternative. The Committee recommended that propylthiouracil should remain on the core list of the EML for use in patients during the first trimester of pregnancy, and for other patients in whom alternative first-

line treatment is not appropriate or available. The square box should be removed from the listing. The Committee also recommended that propylthiouracil should remain on the complementary list of the EMLc for use in patients for whom alternative first-line treatment is not appropriate or available.

The Committee considered that the available evidence indicated that efficacy of methimazole is at least equivalent to propylthiouracil. Compared to propylthiouracil however, methimazole demonstrated a more favourable safety profile with fewer reported major adverse events. The Committee noted that propylthiouracil remains the treatment of choice in some patients and therefore should remain available.

Section 22: MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

22.3 Uterotonics

Carbetocin (heat stable) – addition – EML (ATC Code: H01BB03)

ADDITION: The Committee recommended the addition of heat-stable carbetocin injection to the core list of the EML for the prevention of postpartum haemorrhage on the basis of similar effects compared to oxytocin for efficacy and safety outcomes. The Committee agreed that heat-stable carbetocin may offer advantages over oxytocin in some settings as it does not require cold-chain transport or refrigerated storage.

The Committee noted the current higher cost of carbetocin compared to other uterotonics and agreed with the context-specific recommendation in WHO guidelines for the prevention of PPH, that carbetocin be used where its cost is comparable to other effective uterotonics.

The Expert Committee also recommended that WHO facilitate increased access and affordability of carbetocin through inclusion in the WHO Prequalification of medicines programme.

Mifepristone-misoprostol – change to listing – EML (ATC Codes G03XB01, G02AD06)

CHANGE TO LISTING: The Expert Committee recommended moving mifepristone-misoprostol from the complementary to the core list of the EML, and removal of the note that states that close medical supervision is required, on the basis of the strong evidence presented that close medical supervision is not required for its safe and effective use.

The Committee also recommended the addition of a co-packaged presentation of mifepristone and misoprostol to the core list of the EML.

Recalling that their role and responsibility is to provide WHO with technical guidance in relation to the selection and use of essential medicines, the Expert Committee noted that its mandate does not extend to providing advice on the statement “Where permitted under national law and where culturally acceptable”.

Misoprostol – rejected application for deletion of prevention of post-partum haemorrhage (PPH) – EML (ATC Code G02AD06)

REJECTED APPLICATION: The Committee did not recommend the deletion of the indication for prevention of PPH from the listing of misoprostol from EML. The Committee considered that the new evidence presented in this re-submission was insufficient to support any change to the current listing.

The Committee reiterated that misoprostol remains an effective alternative for prevention of PPH in resource-poor, community and rural settings where oxytocin is unavailable or cannot be safely administered. The listing of misoprostol on the EML supports its appropriate use in such settings and is consistent with the 2018 WHO recommendations for uterotonics for the prevention of PPH.

22.5 Other medicines administered to the mother

Tranexamic acid – new indication treatment of post-partum haemorrhage (PPH) – EML (ATC Code B02AA02)

NEW INDICATION: The Committee recommended listing of tranexamic acid (TXA) intravenous injection on the core list of the EML for the new indication of treatment of post-partum haemorrhage.

While the evidence presented in the application supporting the effectiveness of TXA for this indication was limited and came primarily from a single trial, the Committee considered there was benefit associated with the use of TXA in addition to standard care, when administered within 3 hours of childbirth. The Committee also considered that the use of different medicines with different pharmacological mechanisms of action may be useful in the management of PPH.

The Committee noted that there did not appear to be significant harms or adverse events associated with use of TXA in mothers or newborns, but that evidence was limited. The committee considered that further evidence of safety would be desirable.

Section 24: MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

Methylphenidate – rejected application for addition for the treatment of attention-deficit hyperactivity disorder (ADHD) – EML and EMLc (ATC Code: N06BA04)

REJECTED APPLICATION: The Committee did not recommend the addition of methylphenidate to the complementary list of the EML and EMLc for the treatment of attention-deficit hyperactivity disorder (ADHD) due to concerns regarding the quality and interpretation of the evidence for benefits and harms.

24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders

Escitalopram – rejected application for addition – EML (ATC Code N06AB10)

Fluoxetine – addition of square box – EML (ATC Code N06AB03)

ADDITION OF SQUARE BOX: The Committee recommended the addition of a square box symbol to the current listing of fluoxetine on the core list of the EML for treatment of depressive disorders.

The Committee noted that medicines within the pharmacological class of selective serotonin reuptake inhibitors all have demonstrated efficacy, but can differ in terms of pharmacokinetics, adverse events and drug-interaction profiles. The availability of different SSRIs as essential medicines may be beneficial at country level to expand therapeutic alternatives for patients and support better procurement.

REJECTED APPLICATION: As a consequence of the recommendation for the square box with fluoxetine, the Expert Committee did not recommend the separate addition of escitalopram to the core list of the EML. Escitalopram, and other SSRIs should be considered therapeutically equivalent alternatives to fluoxetine for selection at national level.

Section 25: MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

Tiotropium – addition – EML (ATC Code R03BB04)

ADDITION: The Committee recommended the inclusion of tiotropium with a square box as representative of the pharmacological class of long-acting muscarinic agents (LAMA) to the core list of the EML for use in the treatment of chronic obstructive pulmonary disease (COPD) based on the evidence presented for efficacy in reducing COPD exacerbations, safety and cost-effectiveness.

Section 27: VITAMINS AND MINERALS

Iodine – change to listing – EML and EMLc (ATC Code H03CA)

CORRECTION TO STRENGTH: The Expert Committee recommended that the strength of iodine capsules in the EML and EMLc be corrected to 190 mg, to accurately reflect the quantitative composition as described in the marketing authorization and Summary of Product Characteristics (SmPC).

Multiple micronutrient powders - addition –EMLc (ATC Code B03AE10)

ADDITION: The Committee recommended the addition of multiple micronutrient powders to the core list of the EMLc for the prevention of anaemia in infants and children in populations where anaemia is a public health problem. Use should be in line with the recommendations in current WHO Guidelines for point-of-use fortification of foods.

ANNEX

Table 2 Summary of all <u>additions and extensions of listings</u> on 2019 WHO EML and EMLc

Section	Medicine	EML, EMLc
Section 6: Anti-infective medicines (restructured sections to align AWaRe categorisation)		
6.2	*See separate summary of changes to AWaRe classification section 6.2* – **6.2.1: Access group antibiotics** – **6.2.2: Watch group antibiotics** – **6.2.3: Reserve group antibiotics** – **6.2.4: Antileprosy medicines** – **6.2.5: Antituberculosis medicines**	
	New indications for existing medicines on EML and EMLc *Typhoid and paratyphoid (enteric) fever* Ciprofloxacin (Watch) Ceftriaxone (Watch) Azithromycin (Watch) ***Rejected*** *listing for ofloxacin* *Surgical prophylaxis* Cefazolin (Access) Cefazolin (Access) + metronidazole (Access) Amoxicillin + clavulanic acid (Access) + gentamicin (Access) *Oral and dental infections* Amoxicillin (Access) Phenoxymethylpenicillin (Access)	EML, EMLc
6.2.2	Cefuroxime (surgical prophylaxis – Watch)	EML, EMLc
6.2.3	Ceftazidime + avibactam (Reserve last-resort antibiotic)	EML
	Meropenem + vaborbactam (Reserve last-resort antibiotic)	EML
	Plazomicin (Reserve last-resort antibiotic)	EML
6.2.5	***Anti-tuberculosis medicines - new dispersible tablet formulations*** Cycloserine Ethambutol Ethionamide Isoniazid Levofloxacin Linezolid Moxifloxacin Clofazimine Rifabutin	EMLc
	Bedaquiline (MDR-TB in children and adolescents 6-17 years)	EMLc
	New indication Amoxicillin + clavulanic acid (multidrug-resistant TB)	EML, EMLc

Section	Medicine	EML, EMLc
	New indication Imipenem + cilastatin (multidrug-resistant TB)	EML, EMLc
	New indication Meropenem (multidrug-resistant tuberculosis, MDR-TB)	EML, EMLc
	Isoniazid 100mg dispersible tablet (tuberculosis infants, children)	EMLc
6.4.2	Dolutegravir + lamivudine + tenofovir disoproxil fumarate (fixed-dose combination)	EML
6.4.2.3	Ritonavir oral powder 100mg	EML, EMLc
	Lopinavir + ritonavir oral granules 40 mg + 10 mg fixed-dose combination	EMLc
6.4.2.4	Dolutegravir 50mg tablet (for children weighing 25kg or more)	EMLc
	Raltegravir granules for oral suspension 100 mg	EML, EMLc
6.4.4.2	*Medicines for hepatitis C now differentiates between pangenotypic and non-pangenotypic direct acting antivirals, and other antivirals*	
6.4.4.2.1	*Pangeotypic direct-acting antiviral combinations* Glecaprevir + pibrentasvir This new combination adds to existing pagenotypic combination options on the EML (sofosbuvir + velpatasvir, sofosbuvir/daclatasvir)	EML
6.5.3.2	Sulfadoxine + pyrimethamine (fixed-dose combination; intermittent preventive treatment of malaria in pregnancy (IPTp))	EML
	Sulfadoxine + pyrimethamine (fixed-dose combination; intermittent preventive treatment of malaria in infancy (IPTi))	EMLc
	Amodiaquine and sulfadoxine + pyrimethamine (co-packaged formulations of dispersible tablets; for seasonal malaria chemoprevention)	EMLc
6.5.5.1	Fexinidazole for treatment of 1st and 2nd stages of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.	EML, EMLc
6.6	*Medicines for ectoparasitic infections (new section)* Ivermectin (scabies)	EML, EMLc
Section 8: (Re-named) Immunomodulators and antineoplastics		
8.1	***Anti-TNF biologics for chronic inflammatory conditions*** Adalimumab *Listed with square box with nominated alternatives:* Etanercept, infliximab, certolizumab pegol and golimumab (adults) Etanercept, infliximab (children)	 EML, EMLc EML EMLc
8.2	***Re-named Antineoplastic and supportive agents***	
	All-trans retinoid acid (Acute promyelocytic leukaemia)	EMLc
	Dasatinib (Imatinib-resistant chronic myeloid leukaemia)	EMLc
	Fluorouracil (nasopharyngeal carcinoma, early-stage colon cancer, early-stage rectal cancer, metastatic colorectal cancer)	EMLc
	Imatinib (chronic myeloid leukaemia, gastrointestinal stromal tumour)	EMLc
	Irinotecan (metastatic colorectal cancer)	EMLc
	Nilotinib (imatinib-resistant chronic myeloid leukaemia)	EMLc
	Oxaliplatin (early stage colon cancer, metastatic colorectal cancer)	EMLc
	Procarbazine (Hodgkin lymphoma)	EMLc
	Rituximab (diffuse large B-cell lymphoma)	EMLc
	Enoxaparin (anticoagulant) *Listed with a square box*	EMLc

Section	Medicine	EML, EMLc
	Extension of indications for currently listed cancer medicines for children Bleomycin (Kaposi sarcoma) Doxorubicin (Kaposi sarcoma) Vincristine (Kaposi sarcoma) Cisplatin (Nasopharyngeal carcinoma) Cyclophosphamide (Diffuse large B-cell lymphoma) Prednisolone (Diffuse large B-cell lymphoma) Cytarabine (Acute promyelocytic leukaemia) Daunorubicin (Acute promyelocytic leukaemia) Mercaptopurine (Acute promyelocytic leukaemia) Methotrexate (Acute promyelocytic leukaemia) Cytarabine (Acute myelogenous leukaemia) Hydroxycarbamide (Chronic myeloid leukaemia)	EMLc
8.2.1	Arsenic trioxide (IV formulations; acute promyelocytic leukaemia)	EML, EMLc
	Realgar-Indigo naturalis (containing tetra-arsenic tetra-sulfide 30mg; acute promyelocytic leukaemia)	EML, EMLc
	Extension of indications for currently listed cancer medicines Cisplatin (cervical cancer) Carboplatin (cervical cancer) Paclitaxel (cervical cancer)	EML
	Pegaspargase (acute lymphoblastic leukaemia)	EML, EMLc
	Additional indication cyclophosphamide (multiple myeloma)	EML
	Additional indication doxorubicin (multiple myeloma)	EML
8.2.2	Erlotinib (EGFR mutation positive advanced non-small cell lung cancer) *Listed with square box with nominated alternatives:* afatinib, gefitinib	EML
	Bortezomib (multiple myeloma)	EML
8.2.3	Lenalidomide (multiple myeloma)	EML
	Thalidomide (multiple myeloma)	EML
	Melphalan (multiple myeloma)	EML
	Nivolumab (metastatic melanoma). *Listed with square box with nominated alternative:* pembrolizumab	EML
8.2.4	Abiraterone (metastatic castration-resistant prostate cancer)	EML
	Additional indication prednisone (multiple myeloma)	EML
	Additional indication dexamethasone (multiple myeloma)	EML
Section 10: Medicines affecting the blood		
10.2	Dabigatran *Listed with square box with nominated alternatives:* apixaban, edoxaban, rivaroxaban	EML
Section 12: Cardiovascular medicines		
12.3	Lisinopril + amlodipine (fixed-dose combination) *Listed with square box for ACE inhibitors (lisinopril) and dihydropyridine class of calcium channel blockers (amlodipine)*	EML
	Lisinopril + hydrochlorothiazide (fixed-dose combination)	EML

Section	Medicine	EML, EMLc
	Listed with square box for ACE inhibitors (lisinopril) and thiazide diuretics (hydrochlorothiazide)	
	Telmisartan + amlodipine (fixed-dose combination) *Listed with square box for A2-receptor antagonists (telmisartan) and dihydropyridine class of calcium channel blockers (amlodipine)*	EML
	Telmisartan + hydrochlorothiazide (fixed-dose combination) *Listed with square box for A2-receptor antagonists (telmisartan) and thiazide diuretics (hydrochlorothiazide)*	EML
12.5.2	Alteplase (acute ischaemic stroke)	EML
Section 17: Gastrointestinal medicines		
17.2	Aprepitant (chemotherapy-induced nausea and vomiting)	EML, EMLc
	Ondansetron *listed with square box with nominated alternatives: other 5-HT3 receptor antagonists*	EML, EMLc
17.5	Oral rehydration salts and zinc sulfate tablets (co-packaged)	EMLc
Section 18: Re-named Medicines for endocrine disorders		
18.6	Diazoxide (hypoglycaemia secondary to prolonged hyperinsulinism)	EMLc
18.7	Methimazole *Listed with square box with nominated alternative:* carbimazole	EML, EMLc
Section 19: Immunologicals		
19.3	*Vaccines* Dengue vaccine	EML, EMLc
Section 22: Re-named Medicines for reproductive health and perinatal care		
22.3	Carbocetin (prevention of post-partum haemorrhage)	EML
	Retain Misoprostol (prevention of post-partum haemorrhage)	
	Mifepristone and misoprostol ***Moved*** to Core List; ***Removal*** of the note "Requires close medical supervision; ***Addition*** of co-packaged presentation	EML
22.5	Tranexamic acid (post-partum haemorrhage)	EML
Section 24: Medicines for mental and behavioural disorders		
	Fluoxetine *Listed with square box*	EML
Section 25: Medicines acting on the respiratory tract		
25.1	Tiotropium *Listed with square box with other SSRIs*	EML
Section 27: Vitamins and minerals		
	Iodine *Corrected listed strength to 190mg*	
	Multiple micronutrient powders	

Table 3 Summary of rejected applications to 2019 WHO EML and EMLc

Section	Medicine	EML, EMLc
Section 6: Anti-infective medicines (restructured sections to align AWaRe categorisation)		
6.2	***New indications for existing medicines on EML and EMLc*** *Typhoid and paratyphoid (enteric) fever* ***Rejected*** *listing for ofloxacin*	
6.2.3	***Rejected*** Ceftolozone + tazobactam as last-resort antibiotic	
	Rejected Delafloxacin as last-resort antibiotic	
	Rejected Eravacycline as last-resort antibiotic	
	Rejected Omadacycline as last-resort antibiotic	
6.2.5	***Rejected*** *application for addition of injection formulations* Ethambutol; Isoniazid; p-aminosalicylic acid; Rifampicin	
	Rejected change to age restriction for delamanid (remains 6-17 years)	EMLc
	Rejected Isoniazid liquid (tuberculosis infants, children)	EMLc
Section7: Antimigraine medicines		
	Rejected sumitriptan	EML
Section 8: (Re-named) Immunomodulators and antineoplastics		
8.1	***Rejected*** glatiramer acetate (multiple sclerosis)	
	Rejected fingolimod (multiple sclerosis)	
	Rejected ocrelizumab (multiple sclerosis)	
8.2	***Re-named Antineoplastic and supportive agents***	
	Rejected zoledronic acid	
8.2.1	***Rejected*** Fluorouracil (cervical cancer)	
8.2.2	***Rejected*** pertuzumab (HER-2 positive breast cancer)	
	Rejected subcutaneous formulation of rituximab (diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma)	
	Rejected subcutaneous formulation of trastuzumab (HER-2 positive breast cancer)	
	Rejected trastuzumab emtansine (HER-2 positive breast cancer)	
8.2.3	***Rejected*** atezolizumab (metastatic non-small cell lung cancer)	
	Rejected nivolumab (metastatic non-small cell lung cancer)	
	Rejected pembrolizumab (metastatic non-small cell lung cancer)	
8.2.4	***Rejected*** Enzalutamide (metastatic castration-resistant prostate cancer)	
Section 18: Re-named Medicines for endocrine disorders		
18.5	***Rejected*** Long-acting insulin analogues	
Section 22: Re-named Medicines for reproductive health and perinatal care		
22.3	***Retain*** Misoprostol (prevention of post-partum haemorrhage)	
Section 24: Medicines for mental and behavioural disorders		
	Rejected methylphenidate (attention-deficit hyperactivity disorder, ADHD)	
24.2.1	***Rejected*** escitalopram	

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