Changes to 2017 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 2017 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, 2017 and this summary should be read in conjunction with the full report (WHO Technical Report Series, No. 1006; http://apps.who.int/iris/bitstream/10665/259481/1/9789241210157-eng.pdf?ua=1)

The revised lists of essential medicines (in English) are available as follows:

2017 WHO Model List of Essential Medicines for adults (EML)
http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

2017 Model List of Essential Medicines for children (EMLc)
http://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017_FINAL_amendedAug2017.pdf?ua=1

Table Summary of changes to 2017 WHO EML and EMLc

Section	Medicine	EML, EMLc
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2.1	Paracetamol – new strength oral liquid 120mg/5ml	EML, EMLc
2.2	Fentanyl (cancer pain)	EML
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	Rejected tramadol (cancer pain)	
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	No changes	
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	No changes	
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6.2	*See separate summary of changes to section 6.2*	
6.2.2	Azithromycin (yaws)	EML, EMLc
6.2.4	Clofazimine (multidrug-resistant tuberculosis, MDR-TB)	EML, EMLc
	Delamanid (MDR-TB in children and adolescents 6-17 years)	EMLc
	Rejected gatifloxacin (MDR-TB)	
	Isoniazid + pyrazinamide + rifampicin (fixed-dose combination)	EMLc
	Isoniazid + rifampicin (fixed-dose combination)	EMLc
	Deletion ofloxacin (MDR-TB)	EML, EMLc
	Deletion streptomycin as first-line treatment	EML
6.3	Itraconazole for selected fungal infections	EML, EMLc
	Voriconazole acute invasive aspergillosis, chronic pulmonary aspergillosis	EML, EMLc
6.4.2	***Deletion*** Abacavir oral liquid 100mg/5ml	EML, EMLc
	Deletion Atazanavir solid oral dose form 150mg	EML, EMLc
	Deletion Efavirenz capsule 50mg, 100mg, 200mg	EML, EMLc
	Deletion Lamivudine oral liquid 50mg/ml	EML, EMLc
	Deletion Lamivudine + nevirapine + stavudine tablets	EML
	Deletion Lamivudine + nevirapine + stavudine dispersible tablets	EMLc
	Deletion Nevirapine tablet 200mg	EMLc
	Deletion Stavudine all dose forms/strengths	EML, EMLc
	Deletion Zidovudine capsule 100mg	EML, EMLc
6.4.2.1	Abacavir (dispersible tablet)	EMLc
	Zidovudine (dispersible tablet)	EMLc
6.4.2.3	Atazanavir + ritonavir (fixed-dose combination)	EML
	Lopinavir + ritonavir *(*fixed-dose combination)	EMLc
6.4.2.4	Dolutegravir	EML

Section	Medicine	EML, EMLc
	Raltegravir	EML, EMLc
	Abacavir + lamivudine (fixed-dose combination)	EMLc
	Rejected Cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide	
	Efavirenz + lamivudine + tenofovir disoproxil fumarate (fixed-dose combination)	EML
	Rejected Emtricitabine + tenofovir alafenamide	
	Rejected Emtricitabine + rilpivirine + tenofovir alafenamide	
	Tenofovir disoproxil fumarate (pre-exposure prophylaxis)	EML
	Emtricitabine + tenofovir disoproxil fumarate (pre-exposure prophylaxis)	EML
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6.4.2.5	Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	EML, EMLc
6.4.3	***Retain*** Oseltamivir	EML, EMLc
6.4.4.1.1.	***Rejected*** Tenofovir alafenamide	
6.4.4.2	***Rejected*** Elbasvir + grazoprevir	
	Sofosbuvir + velpatasvir	EML
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	Dihydroartemisinin + piperaquine (fixed-dose combination)	EML, EMLc
Section7: Antimigraine medicines		
	No changes	
Section 8: Anti-neoplastics and immunosuppressives		
8.2	***Rejected*** Erlotinib, gefitinib, afatinib, crizotinib	
	Nilotinib	EML
	Dasatinib	EML
	Rejected Trastuzumab emtansine	
	Zoledronic acid	EML
8.3	***Rejected*** Enzalutamide	
Section 9: Antiparkinsonism medicines		
	No changes	
Section 10: Medicines affecting the blood		
10.1	Erythropoietin	EML, EMLc
	Darbopoetin alfa	EML, EMLc
	Methoxy polyethylene glycol-epoetin beta	EML, EMLc
Section 11: Blood products of human origin and plasma substitutes		
	No changes	
Section 12: Cardiovascular medicines		
12.3	***Rejected*** Lisinopril + hydrochlorothiazide (fixed-dose combination)	
	Losartan	EML
12.7	***Rejected*** Aspirin + atorvastatin + ramipril (fixed-dose combination)	
Section 13: Dermatological medicines (topical)		
	No changes	
Section 14: Diagnostic agents		
	No changes	
Section 15: Disinfectants and antiseptics		

Section	Medicine	EML, EMLc
15.1	***Rejected*** Hypochlorous acid solution and hydrogel	
Section 16: Diuretics		
	No changes	
Section 17: Gastrointestinal medicines		
	No changes	
Section 18: Hormones, other endocrine medicines and contraceptives		
18.3.1	Ulipristal acetate	EML
18.3.2	Medroxyprogesterone acetate (subcutaneous formulation)	EML
18.5	***Rejected*** Long-acting insulin analogues	
	Rejected Second-line treatments for type 2 diabetes	
Section 19: Immunologicals		
	No changes	
Section 20: Muscle relaxants (peripherally-acting) and cholinesterase inhibitors		
	No changes	
Section 21: Ophthalmological preparations		
21.1	Natamycin	EML, EMLc
21.6	***Retain*** Bevacizumab	EML
Section 22: Oxytocics and antioxytocics		
22.1	***Retain*** Misoprostol (prevention of post-partum haemorrhage)	EML
Section 23: Peritoneal dialysis solution		
	No changes	
Section 24: Medicines for mental and behavioural disorders		
	No changes	
Section 25: Medicines acting on the respiratory tract		
25.1	Budesonide + formoterol (combination inhaler)	EML
	Rejected Budesonide + formoterol (combination inhaler, children)	
Section 26: Solutions correcting water, electrolyte and acid–base disturbances		
26.3	***Rejected*** Ready to use therapeutic food (RUTF)	
Section 27: Vitamins and minerals		
	No changes	
Section 28: Ear, nose and throat medicines		
	No changes	
Section 29: Specific medicines for neonatal care		
	No changes	
Section 30: Medicines for diseases of joints		
	No changes	

Section 1: Anaesthetics, preoperative medicines and medical gases

1.4: Medical gases (new section)

Oxygen – extension of listing in EML and EMLc (ATC Code: V03AN01)

The Expert Committee recommended extending the current listing of oxygen on the EML and EMLc to include management of hypoxaemia, in addition to its current listing as an inhalational medicine in general anaesthesia. The new listing is recommended to be in a new section, 1.4 Medical gases.

Section 2: Medicines for pain and palliative care

2.1: Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

Paracetamol – addition of new strength of oral liquid – EML and EMLc (ATC Code: N02BE01)

The Expert Committee recommended the addition of the new strength of paracetamol oral liquid, 120 mg/5 mL to the EML and EMLc, noting its wider global market availability than the currently listed 125 mg/5 mL strength.

2.2: Opioid analgesics

Fentanyl (addition for management of cancer pain) – EML (ATC Code: N02AB03)

The Expert Committee accepted that there is a need for additional opioid options for treatment of pain in cancer patients. The Committee therefore recommended the addition of transdermal fentanyl to the EML for treatment of cancer pain.

The Committee did not recommend transdermal fentanyl for inclusion on the EMLc because of adverse effects and concerns regarding overdosing.

The Committee noted the potential for harms, misuse and abuse associated with residual fentanyl in used patches and appropriate, safe disposal of used patches is essential.

Methadone (addition for management of cancer pain) EML and EMLc (ATC Code: N07BC02)

The Expert Committee accepted that there is a need for additional opioid treatment options for cancer pain patients. The Committee considered that methadone can be a suitable inexpensive and widely available treatment alternative to morphine.

The Committee noted that countries may require training in the use of methadone and therefore recommended the additional indication of methadone on the Complementary List to the EML and a new addition to the Complementary List of the EMLc for the treatment of cancer pain.

Tramadol (rejected application for addition for cancer pain) – EML and EMLc (ATC Code: N02AX02)

REJECTED APPLICATION: The Committee acknowledged the issues relating to availability of morphine in LMICs, and the differences in the controls to which morphine and tramadol are subject.

The Expert Committee considered that the evidence presented in the application shows tramadol to be a suboptimal treatment for cancer pain compared with morphine and other opioids. The Expert Committee therefore did not recommend the addition of tramadol as a treatment for cancer pain to the EML or EMLc.

2.3: Medicines for other common symptoms in palliative care

Gabapentin – rejected application for management of neuropathic pain (central and peripheral) in adults – EML (ATC Code: N03AX12)

REJECTED APPLICATION: The Expert Committee considered the uncertainty in efficacy estimates as a result of publication and outcome reporting biases in the currently available evidence for gabapentin.

The Committee did not recommend inclusion of gabapentin on the EML for neuropathic pain because of its uncertain benefits.

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

Lamotrigine - addition for treatment-resistant partial or generalized epileptic seizures – EML and EMLc (ATC Code: N03AX09)

The Expert Committee noted that lamotrigine has been shown to be effective as an adjunctive therapy for persons with partial or generalized epileptic seizures refractory to monotherapy with one of the antiepileptic drugs already included in the EML/EMLc. The Committee also noted that lamotrigine has been reported to be a valid alternative to carbamazepine and valproate as monotherapy. Its safety profile for use in women of childbearing age and people living with HIV/AIDS appears favourable compared with other therapeutic options included in the EML/EMLc.

Considering all relevant clinical outcomes, there is a net benefit, resulting primarily from the safety profile of lamotrigine. Based on the positive evaluation, the Expert Committee 53 Applications for the 20th EML and the 6th EMLc recommended that lamotrigine be included in the EML and EMLc as an adjunctive therapy for persons with partial or generalized epileptic seizures refractory to monotherapy with one of the antiepileptic drugs already included in the EML/EMLc.

The Committee recommended that a review of the effectiveness and safety of lamotrigine in comparison with other alternatives (e.g. levetiracetam) would be informative for a future EML application.

Section 6: Anti-infective medicines

6.1: Anthelminthics

6.1.1: Intestinal anthelminthics

Ivermectin – new indication against Strongyloides stercoralis and soil-transmitted helminthiasis (STH) – *EML and EMLc (ATC Code: P02CF01)*

The Expert Committee acknowledged the favourable benefit–harm ratio and the public health impact of ivermectin in the treatment of intestinal helminth infections.

The Committee recommended adding ivermectin to the EML and EMLc under Section 6.2.1 Intestinal anthelminthics for use against Strongyloides stercoralis and STH. It may be used in combination with albendazole for treatment of STH.

6.2: Antibacterials

Comprehensive review of antibiotics – EML and EMLc. SEE SEPARATE SUMMARY OF CHANGES TO SECTION 6.2

6.2.2: Other antibacterials

The Expert Committee acknowledged the favourable benefit-harm ratio of single-dose azithromycin as the treatment of choice for yaws and that it is recommended as part of the WHO strategy for yaws eradication. The Committee therefore recommended that the indications for azithromycin on the EML and EMLc be extended to include single-dose treatment of yaws.

Azithromycin – new indication for the treatment of yaws – EML and EMLc (ATC Code: J01FA10)

6.2.4: Antituberculosis medicines

Clofazimine – new indication as reserve second-line drug for the treatment of multidrug-resistant tuberculosis (*MDR-TB) – EML and EMLc (ATC Code: J04BA01)*

The Expert Committee acknowledged that the updated WHO guidelines for the management of multidrug-resistant tuberculosis now include clofazimine as a Group C medicine and as part of the new short-course regimen.

Recognizing the significant public health need for effective treatments for MDR/XDR-TB, the Committee recommended that the indications for clofazimine on the EML and EMLc be extended to include the new indication of MDR-TB. In keeping with other listings for second-line drugs for MDR-TB, the Committee recommended clofazimine be included on the Complementary List for this indication.

Delamanid – reserve second-line drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) in children and adolescents aged 6–17 years – EMLc (ATC Code: J04AK06)

The Expert Committee recommended the addition of delamanid to the complementary list of the EMLc as a reserve second-line drug for the treatment of multidrug-resistant tuberculosis in children and adolescents aged 6–17 years. The Committee noted that evidence for use of delamanid in paediatric patients is limited but that there is a global need for effective new oral treatments for MDR-TB for children.

As for the listing of delamanid for adults in 2015, the Expert Committee recommended that delamanid for the treatment of children should be introduced only in settings where close monitoring of patients and active pharmacovigilance can be ensured.

Gatifloxacin – <u>rejected</u> application for addition as a reserve second-line drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) – EML and EMLc

REJECTED APPLICATION: The Expert Committee did not recommend the addition of gatifloxacin to the complementary list of the EML and EMLc as a reserve second-line drug for the treatment of multidrug-resistant tuberculosis. The Committee noted that gatifloxacin, in short therapy regimens, did not show superiority in benefit–harm ratio to alternative fluoroquinolones currently listed on the EML and EMLc (levofloxacin and moxifloxacin).

Isoniazid + pyrazinamide + rifampicin – new formulation fixed-dose combination – EMLc (ATC Code: J04AM05)

Isoniazid + rifampicin – new formulation fixed dose combination – EMLc (ATC Code: J04AM02)

The Expert Committee recommended the addition to the core list of the EMLc of two fixed-dose combination (FDC), child-friendly formulations for the treatment of children less than 25 kg with tuberculosis: isoniazid + pyrazinamide + rifampicin for use in the intensive phase; and isoniazid + rifampicin for use in the continuation phase of treatment.

The Committee considered that the availability of these age-appropriate FDC formulations for treatment

of tuberculosis in children would offer benefits, including appropriate dosing, ease of administration and reduced pill burden, and could contribute to better therapeutic adherence.

Ofloxacin – deletion as reserve second-line medicine for the treatment of multidrug-resistant tuberculosis (MDR-TB) – EML and EMLc (ATC Code: J01MA01)

DELETION: Noting that ofloxacin is no longer recommended in updated WHO guidelines, the Expert Committee recommended the deletion of ofloxacin (as an alternative to levofloxacin) from the complementary list of the EML and EMLc as a reserve second-line medicine for the treatment of multidrug-resistant tuberculosis.

Streptomycin – deletion as first-line antituberculosis medicine – EML (ATC Code: J01GA01)

DELETION: The Expert Committee recommended the deletion of streptomycin powder for injection from the core list of the EML as a first-line antituberculosis treatment option, noting the advice from the WHO TB department that it is no longer recommended as first-line treatment.

The Committee noted that streptomycin remains in the complementary list of the EML and EMLc for second-line use in multidrug-resistant tuberculosis.

6.3: Antifungal medicines

Itraconazole – addition for selected fungal infections – EML and EMLc (ATC Code: J02AC02)

The Expert Committee recommended the addition of itraconazole to the EML and the EMLc for treatment of chronic cavitary pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, infections caused by *Talaromyces marneffei* and chromoblastomycosis, and for prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients. The Committee did not recommend the inclusion of the indication of acute invasive aspergillosis for itraconazole, noting that voriconazole is the current treatment of choice.

The Committee recommended that, with the addition of new azoles (itraconazole and voriconazole) to the Model Lists, the square box should be removed from the current listing for fluconazole.

Voriconazole – addition for acute invasive aspergillosis and chronic pulmonary aspergillosis – EML and EMLc (ATC Code: J02AC03)

The Expert Committee recommended the addition of voriconazole to the EML and EMLc for the treatment of acute invasive aspergillosis and chronic pulmonary aspergillosis. The Committee acknowledged that voriconazole is currently the recommended treatment of choice for acute invasive aspergillosis in available guidelines.

The Committee recommended that, with the addition of new azoles (itraconazole and voriconazole) to the Model Lists, the square box should be removed from the current listing for fluconazole.

6.4: Antiviral medicines

6.4.2: Antiretrovirals

DELETION of ARV formulations from EML and EMLc

WHO Department of HIV/AIDS 2017 requested deletion of a number of ARV formulations as the medicine was (i) not recommended as a therapeutic option in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, or (ii) d*ose in the current EML is not aligned with the recommended dosing in the 2016 WHO Consolidated guidelines, or (iii) to provide alignment with the optimal Formulary of the Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Their Children.

The Expert Committee noted that lamivudine oral liquid is still recommended in the 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* for the treatment of newborns, and on this basis it is retained on the EMLc.

The medicines and formulations deleted from the EML and EMLc are shown in the following table.

Deletion of ARV formulations from EML and EMLc

Medicine	***Dose form/strength/formulation***	***Delete EML***	***Delete EMLc***
abacavir	Oral liquid: 100 mg (as sulfate)/5 mL	x	x
efavirenz	Capsule: 50 mg, 100 mg, 200 mg	x	x
lamivudine	Oral liquid: 50 mg/mL	x	-
stavudine	Capsule: 15 mg; 20 mg; 30 mg	x	x
	Powder for oral liquid: 5 mg/mL	x	x
zidovudine	Capsule: 100mg	x	x
atazanavir	Solid oral dose form: 150mg	x	x
lamivudine + nevirapine + stavudine	Tablet: 150mg + 200mg + 30mg	x	N/A
	Tablet (dispersible): 30mg + 50mg + 6mg	x	x
nevirapine	Tablet : 200mg	-	x
saquinavir	Solid oral dose form : 200mg; 500mg (as mesylate)	x	N/A
zidovudine	Solution for IV infusion injection: 10mg/mL in 20-mL vial	x	N/A

6.4.2.1: Nucleoside/Nucleotide reverse transcriptase inhibitors

Abacavir – addition of new formulation and strength (dispersible tablet) for treatment of children with HIV infection – EMLc (ATC Code: J05AF06)

Taking into account the recommendations for abacavir in current WHO HIV treatment guidelines and the decision taken in parallel at this meeting to delete abacavir oral liquid from the EML and EMLc, the Expert Committee recommended the addition of the proposed 60-mg dispersible, scored tablet formulation of abacavir to the core list of the EMLc, noting the importance of the availability of effective, age-appropriate paediatric dosage forms of antiretroviral medicines.

Zidovudine (ZDV or AZT) – addition of new formulation and strength (dispersible tablet) for treatment of children with HIV infection – EMLc (ATC Code: J05AF01)

Taking into account the recommendations for zidovudine in current WHO HIV treatment guidelines and the decision taken in parallel at this meeting to delete zidovudine 100-mg capsules from the EML and EMLc, the Expert Committee recommended the addition of the proposed 60-mg dispersible, scored tablet formulation of zidovudine to the core list of the EMLc, noting the importance of the availability of effective, age-appropriate paediatric dosage forms of antiretroviral medicines.

6.4.2.3: Protease inhibitors

Atazanavir + ritonavir – addition of fixed-dose combination – EML (ATC Code: to be assigned)

The Expert Committee recommended the addition of the fixed-dose combination of atazanavir + ritonavir to the core list of the EML. The Committee noted that ATV/r is recommended in current WHO HIV treatment guidelines as a preferred protease inhibitor for second-line treatment of adults, adolescents and pregnant or breastfeeding women, in combination with a nucleoside reverse transcriptase inhibitor backbone.

Lopinavir + ritonavir – new formulation and strength (fixed-dose combination) for children with HIV infection – EMLc (ATC Code: J05AR10)

The Expert Committee recommended the addition of the new formulation and strength of a fixed-dose combination of lopinavir + ritonavir to the EMLc for treatment of children aged 3 months to 3 years.

The Committee considered that age-appropriate fixed-dose combinations for antiretroviral therapy offer benefits including greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

6.4.2.4: Integrase inhibitors – new subsection

Dolutegravir – addition – EML (ATC Code: J05ZA12)

The Committee noted that dolutegravir is recommended as a first-line antiretroviral treatment option in current WHO HIV treatment guidelines and is included on the List of Prequalified Medicinal Products; access could be improved via generic licensing agreements through the Medicines Patent Pool (e.g. nine generic manufacturers have taken generic licences and three have applied for WHO prequalification).

Taking into consideration the evidence that dolutegravir is an effective first-line HIV treatment option and its acceptable safety profile, the Expert Committee recommended the addition of dolutegravir to the core list of the EML in a new subsection for integrase inhibitors.

Raltegravir – addition – EML and EMLc (ATC Code: J05AX08)

The Expert Committee recommended the inclusion of raltegravir in the core list of the EML for use in pregnant women and in the core list of the EMLc as a second-line treatment option for children in accordance with WHO guidelines. The Committee considered that dolutegravir was the preferred integrase inhibitor for most patients, but noted that no data currently exist for the use of dolutegravir in pregnant women and children.

Abacavir + lamivudine – addition of a new strength (fixed-dose combination) for children with HIV infection – EMLc (ATC Code: J05AR02)

The Expert Committee recommended the addition of the new strength of a fixed-dose combination of abacavir + lamivudine to the EMLc.

The Committee noted that abacavir + lamivudine is recommended in current HIV treatment guidelines as a nucleoside reverse transcriptase inhibitor backbone of first-line antiretroviral regimens for infants and children under 3 years of age and is the preferred NRTI backbone for children aged 3–10 years.

The Committee considered that that the availability of age-appropriate FDC ART formulations offer the benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

Cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide – rejected application for addition – EML (ATC Code: J05AR18)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of the fixed-dose combination formulation of cobicistat, elvitegravir, emtricitabine and tenofovir alafenamide to the core list of the EML for treatment of HIV infection in ART-naive adults and children aged 12 years and above. The Committee noted the suggestion of a better safety profile associated with the TAF combination compared with the corresponding TDF combination but considered this to be of uncertain patient-relevant benefit in the long term (as the benefits were based on surrogate outcome measures). The Committee also noted concerns regarding potential drug–drug interactions of this combination with other medicines, particularly rifampicin.

The Committee noted that the TAF combination is not recommended as first-line ART in WHO

guidelines. The Committee recalled that a similar TDF-based formulation was not recommended for inclusion on the EML in 2015 on the basis that no clinical advantage over currently recommended formulations had been demonstrated.

Efavirenz + lamivudine + tenofovir disoproxil fumarate – addition of fixed-dose formulation – EML (ATC Code : J05AR11)

The Expert Committee recommended a new formulation of efavirenz + lamivudine + tenofovir disoproxil fumarate for inclusion in the EML. The Committee noted the favourable benefit–risk profile for the lower-strength efavirenz combination: efavirenz 400-mg combinations were found to be non-inferior to combinations with higher efavirenz doses (600 mg) in terms of efficacy, with reduced toxicity. The Committee also noted that EFV400 + 3TC (or FTC) + TDF is included in the latest WHO HIV treatment guidelines infection as an alternative first-line treatment option for adults and adolescents.

As previously, the Committee considered that the availability of FDC ART formulations offer benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

Emtricitabine + tenofovir alafenamide – rejected application for addition – EML (ATC Code: J05AR17)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of the fixed-dose combination formulation of emtricitabine and tenofovir alafenamide to the core list of the EML for treatment of HIV infection in adults and children aged 12 years and older.

The Committee noted the suggestion of a better safety profile associated with the TAF combination compared with the corresponding TDF combination but considered this to be of uncertain patient-relevant benefit in the long term (as the benefits were based on surrogate outcome measures). The Committee also noted concerns regarding potential drug–drug interactions of this combination with other medicines, particularly rifampicin.

The Committee noted that the TAF combination is not recommended as first-line ART in current WHO guidelines.

Emtricitabine + rilpivirine + tenofovir alafenamide – rejected application for addition – EML (ATC Code: J05AR19)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of a fixed-dose combination formulation of emtricitabine, rilpivirine and tenofovir alafenamide to the core list of the EML for the treatment of HIV infection in patients aged 12 years and above who are antiretroviral treatment-naive and have HIV1-RNA $\leq$100 000 copies/mL.

The Committee noted that the FDC is not recommended as first-line ART in WHO guidelines and recalled that a similar TDF-based formulation had not been recommended in 2015 for inclusion on the EML on the basis of no clinical advantage over currently recommended formulations being demonstrated. The Committee also noted concerns regarding potential drug–drug interactions of this combination with other medicines, particularly rifampicin.

Tenofovir disoproxil fumarate – new indication (pre-exposure prophylaxis) – EML (ATC Code : J05AF07)

Emtricitabine + tenofovir disoproxil fumarate– new indication (pre-exposure prophylaxis) – EML (ATC Code : J05AR03)

Lamivudine + tenofovir disoproxil fumarate– new indication (pre-exposure prophylaxis) – EML (ATC Code : J05AR12)

The Expert Committee recommended the additional indication for single-agent tenofovir disoproxil fumarate (TDF) and the fixed-dose combinations of emtricitabine + TDF (and lamivudine + TDF as an alternative, where FTC is not available) on the EML for use as pre-exposure prophylaxis (PrEP) of HIV infection.

The Committee noted evidence of reduced risk of HIV infection associated with TDF-containing PrEP in study populations demonstrating high adherence to therapy, and the recent inclusion of oral PrEP containing TDF in WHO guidelines for patients at substantial risk of HIV infection.

6.4.2.5: Medicines for prevention of HIV-related opportunistic infections – new subsection

Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim – addition of fixed-dose combination – EML and EMLc (ATC Code: to be assigned)

The Expert Committee recommended the inclusion of the fixed-dose combination formulation of isoniazid, pyridoxine, sulfamethoxazole and trimethoprim (co-trimoxazole) on the core list of the EML and EMLc. Listing was recommended in a new subsection (6.4.2.5) for medicines for the prevention of HIV-related opportunistic infections.

The Committee considered that the availability of FDC formulations offers the benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence. The Committee also noted the direct evidence supporting effectiveness of the FDC from the REALITY trial. The FDC was based on well-established dosing combinations.

6.4.3: Other antivirals

Oseltamivir – change from core to complementary list – EML and EMLc (ATC Code: J05AH02)

RETAIN EML AND EMLc: The Expert Committee noted that oseltamivir was originally listed on the EML during the public health emergency of the 2009 H1N1 influenza outbreak.

The Committee noted that there is now additional evidence regarding the efficacy and safety of oseltamivir therapy for influenza in seasonal and pandemic influenza. The new evidence indicates that the effect of oseltamivir on relevant outcomes of hospital admissions and mortality is lower than previously estimated.

The Committee recognized that oseltamivir is currently the only listed option for critically ill hospitalized patients and for pandemic influenza preparedness. It therefore recommended that oseltamivir be

retained on the EML and EMLc but be moved to the complementary list, for use only in severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.

The Committee also recommended that the next Expert Committee consider oseltamivir for deletion unless new information supporting its use in seasonal and pandemic outbreaks is provided. The Committee agreed that there is a need for further independent studies of oseltamivir in these areas.

The Expert Committee noted that a new WHO guideline on clinical management of severe influenza is currently under development.

6.4.4: Antihepatitis medicines

6.4.4.1: Medicines for hepatitis B

6.4.4.1.1: Nucleoside/Nucleotide reverse transcriptase inhibitors

Tenofovir alafenamide – rejected application for addition – EML (ATC Code: J05AF13)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of tenofovir alafenamide to the core list of the EML for the treatment of chronic hepatitis B infection in adults with compensated liver disease.

The Committee noted the suggestion of a better safety profile for TAF compared with TDF in terms of renal and bone toxicity (based on surrogate markers) but considered this to be of uncertain patient-relevant benefit in the long term. The Committee also noted that TAF is not currently included in WHO guidelines.

6.4.4.2: Medicines for hepatitis C

Elbasvir + grazoprevir – rejected application for addition – EML (ATC Code: J05AX68)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of the fixed-dose combination of elbasvir + grazoprevir to the core list of the EML for the treatment of chronic hepatitis C virus infection, genotype 1 or 4, in adults. Given the current (and potential future) availability of alternative pan-genotypic direct-acting antiviral combinations, the Committee gave priority to the pangenotypic combinations and recommended listing of sofosbuvir + velpatasvir in preference to the elbasvir + grazoprevir combination. The Committee also noted that the guidance from WHO on hepatitis C will shortly be updated.

Sofosbuvir + velpatasvir – addition – EML (ATC Code: J05AX69)

The Expert Committee recommended the addition of the fixed-dose combination of sofosbuvir + velpatasvir to the core list of the EML for the treatment of chronic hepatitis C virus infection on the basis of a favourable benefit–risk ratio. The Committee noted that this is the first pan-genotypic direct-acting antiviral combination to be approved.

6.5: Antiprotozoal medicines

6.5.3: Antimalarial medicines

6.5.3.1: For curative treatment

Artesunate + pyronaridine – addition of fixed-dose combination – EML and EMLc (ATC Code: P01BF06)

The Expert Committee recommended the addition of a fixed-dose combination formulation of artesunate and pyronaridine tetraphosphate to the core list of EML and EMLc as an artemisinin-combination treatment option for the first-line treatment of uncomplicated *Plasmodium falciparum* and for the blood stages of *P. vivax* malaria in adults, children and infants, on the basis of a favourable benefit–risk ratio. Availability of this FDC will provide an alternative treatment option to mefloquine- or amodiaquine-containing combinations.

The Committee considered that that the availability of FDC formulations for treatment of malaria can offer the benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

Artesunate – addition of new strength rectal dose form for children – EMLc (ATC Code: P01BE03)

The Expert Committee recommended addition of the new strength formulation of rectal artesunate to the EMLc for pre-referral treatment of severe malaria.

The Committee accepted that the 100-mg formulation can offer an age-appropriate and suitable treatment option for children weighing 5–14 kg.

Dihydroartemisinin + piperaquine – addition of fixed-dose combination – EML and EMLc (ATC Code: P01BF05)

The Expert Committee recommended the inclusion of dihydroartemisinin + piperaquine phosphate in the core list of the EML and EMLc for use in malaria. The Committee noted both the favourable benefit–risk profile of the combination and its inclusion in the latest WHO guidelines for malaria. The product is safe and efficacious in pregnancy.

Availability of this fixed-dose combination will provide an alternative treatment option to mefloquine- or amodiaquine-containing combinations.

The Committee considered that that the availability of fixed-dose combination formulations for treatment of malaria can offer the benefits of greater dosing accuracy, ease of administration and reduced pill burden and contribute to better therapeutic adherence.

Section 7: Antimigraine medicines

No changes

Section 8: Antineoplastics and immunosuppressives

8.2: Cytotoxic and adjuvant medicines

Note: The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options, across treatment lines. The working group should support WHO in establishing some guiding principles in relation to the potential inclusion of second-line treatments, clarifying what constitutes a clinically relevant therapeutic effect that is sufficient for a cancer medicine to be granted the status of essential medicine.

Erlotinib, (ATC Code: L01XE03); Gefitinib, (ATC Code: L01XE02); Afatinib, (ATC Code: L01XE13); Crizotinib (ATC Code: L01XE16) rejected application for addition – EML

REJECTED APPLICATION: The Expert Committee noted that presentation of the evidence in the application was unsatisfactory: the application did not follow the standard template, and some important elements of the evaluation were missing or inadequately addressed.

Applications in general would benefit from greater focus on the benefits and harms associated with the medicines that are to be evaluated. Extensive search of available evidence is preferable to selective inclusion of some studies. Data from trials and reviews should be summarized in the application, and transparent descriptions of the limitations of the evidence should be provided.

Applications should provide the key information to allow evaluation of the merits of medicines proposed for the EML relative to those already listed. Information should be quantified, in forms that facilitate the assessment of benefits and harms.

The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options, across treatment lines. The working group should support WHO in establishing some guiding principles in relation to the potential inclusion of second-line treatments, clarifying what constitutes a clinically relevant therapeutic effect – and one that is sufficient for a cancer medicine to be granted the status of essential medicine.

The Committee considered that epidermal growth factor receptor tyrosine kinase inhibitors and the anaplastic lymphoma kinase inhibitor may be a valid treatment option for use in patients with non-small cell lung cancer. Erlotinib, gefitinib and afatinib are associated with a more favourable tolerability profile and comparable efficacy to cytotoxic chemotherapy, and crizotinib has been associated with greater efficacy in terms of progression-free and overall survival compared with chemotherapy.

However, the need to screen patients to determine suitability for treatment must be taken into account by health systems. The availability, affordability and quality of diagnostic screening of patients for epidermal growth factor receptor mutations and anaplastic lymphoma kinase gene rearrangements will be an important factor requiring consideration by the working group in prioritizing cancer therapies for future EML applications.

The Expert Committee therefore recommended that erlotinib, gefitinib, afatinib and crizotinib should not be added to the EML at this time, but should be reconsidered as part of a high-quality review

considering a wider spectrum of options in non-small cell lung cancer at its next meeting.

Nilotinib, (ATC Code: L01XE08); Dasatinib (ATC Code: L01XE06) – addition – EML

The Expert Committee noted that the application did not follow the standard template and that some important elements of the evaluation were missing or inadequately addressed.

Despite these shortcomings, the Expert Committee considered that nilotinib and dasatinib have been shown to be valid treatment options for use in patients with chronic myeloid leukaemia and imatinib resistance. Considering all relevant clinical outcomes, the Committee accepted that there is a relevant clinical benefit resulting primarily from large response rates (i.e. complete cytogenetic response) in patients with otherwise very limited treatment options (e.g. donor stem cell transplant).

Based on this overall positive evaluation, the Committee recommended that nilotinib and dasatinib be included on the Complementary List of the EML and EMLc for treatment of CML in patients who are resistant to imatinib.

The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options, across treatment lines. The working group should support WHO in establishing some guiding principles in relation to the potential inclusion of second-line treatments, clarifying what constitutes a clinically relevant therapeutic effect that is sufficient for a cancer medicine to be granted the status of essential medicine.

Trastuzumab emtansine – rejected application for addition – EML (ATC Code: L01XC14)

REJECTED APPLICATION: The Expert Committee acknowledged the significant public health burden of breast cancer, which afflicts an increasing number of people in all countries, irrespective of income.

In addition to trastuzumab emtansine, the Expert Committee noted the availability of other innovative medicines for this condition (e.g. pertuzumab) and of other medicines mentioned in this and previous applications (e.g. lapatinib) which have never been proposed for evaluation for inclusion on the EML. These medicines should be compared with the standard of care and evaluated as potential essential medicines. The outcome of this comparative evaluation will support countries to better understand the additional value and implications of adding them to national EMLs.

While acknowledging the quality of the application in presenting evidence to support the listing of trastuzumab emtansine, the Committee nevertheless recommended that it should not be added to the EML at this time but should be considered at its next meeting as part of a comprehensive review encompassing additional medicines (e.g. pertuzumab, lapatinib, bevacizumab).

The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options, across treatment lines and including recently approved medicines. The working group should support WHO in establishing guiding principles, clarifying what constitutes a clinically relevant therapeutic effect, for granting the status of essential medicine to a cancer medicine, taking into consideration various lines of therapy.

Zoledronic acid – addition – EML (ATC Code: M05BA08)

In relation to the application, the Expert Committee noted that it did not follow the standard template, and some important elements of the evaluation were missing or inadequately addressed.

Despite these shortcomings, the Expert Committee considered that zoledronic acid has been shown to be a valid treatment option for use in patients with malignancy-related bone disease. Based on the positive evaluation, the Committee recommended zoledronic acid be added to the Complementary List of the EML for this indication. The Committee did not recommend listing with a square box, as it considered the evidence presented in the application for alternative bisphosphonates was not adequate to support their inclusion on the EML.

The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options for different cancers. In particular, noting the role of zoledronic in the management of bone metastases associated with multiple myeloma, and that multiple myeloma was not included in the 2015 review of cancer medicines on the EML, the Committee highlighted the need for the working group to evaluate treatments for multiple myeloma as a priority for EML inclusion.

8.3: Hormones and antihormones

Enzalutamide – <u>rejected</u> application for addition – EML – prostate cancer (ATC Code: L02BB04)

REJECTED APPLICATION: The Expert Committee acknowledged the significant public health burden of prostate cancer, which afflicts an increasing number of people in all countries.

The Committee noted the availability of other medicines (e.g. abiraterone), associated with similar survival advantages but not proposed for evaluation for inclusion on the EML. For this reason, a comprehensive evaluation of alternatives, potentially associated with survival gains, should be considered a priority. A comprehensive evaluation of prostate cancer treatment options will support countries, helping them to have a better understanding of the additional value and implications of selection of these medicines for national EMLs.

The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options, including recently approved medicines. The working group should support WHO in establishing guiding principles, clarifying what constitutes a clinically relevant therapeutic effect, for granting the status of essential medicine to a cancer medicine.

While acknowledging the good quality of the application in presenting evidence to support the listing of enzalutamide, the Committee nevertheless recommended that enzalutamide should not be added to the EML at this time but should be considered at its next meeting as part of a comprehensive review encompassing additional medicines (e.g. abiraterone).

Section 9: Antiparkinsonism medicines

No changes

Section 10: Medicines affecting the blood

10.1: Antianaemia medicines

Erythropoiesis-stimulating agents – addition – EML and EMLc

Erythropoietin (ATC Code: B03XA01); Darbopoetin alfa (ATC Code: B03XA02); Methoxy polyethylene glycol-epoetin beta (ATC Code: B03XA03)

The Expert Committee noted that erythropoiesis-stimulating agents have been shown to be an effective medication for treating anaemia in children, young people and adults with chronic renal disease requiring dialysis and that there are no alternative medicines already included in the EML and EMLc for this indication. It also noted that biosimilars for erythropoiesis-stimulating agents have been shown to be a valid alternative to the reference products.

Considering all important clinical outcomes, the Committee considered that there is a relevant benefit resulting from erythropoiesis-stimulating agents. Based on the positive evaluation, the Committee therefore recommended erythropoiesis-stimulating agents be included in the complementary list of the EML and EMLc.

The Expert Committee recommended listing erythropoiesis-stimulating agents with a square box to represent the class and inclusion of a note limiting alternatives to epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta and their respective biosimilars (EML) and epoetin alfa, beta and theta, darbepoetin alfa, and their respective biosimilars (EMLc).

Section 11: Blood products of human origin and plasma substitutes

No changes

Section 12: Cardiovascular medicines

12.3: Antihypertensive medicines

Lisinopril + hydrochlorothiazide – <u>rejected</u> application for addition of fixed-dose combination – EML (ATC Code: C09BA03)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of the proposed fixed-dose combination formulation of lisinopril and hydrochlorothiazide to the core list of the EML for treatment of hypertension in patients not adequately controlled with monotherapy. While it recognized that listing a single FDC of medicines for treatment of hypertension would limit choice from the variety of combinations, components and dosages available that would be necessary to tailor therapy for individual patients, the Committee acknowledged that appropriate FDCs may offer some advantages over the single medicines given concomitantly in terms of adherence and reduced pill burden. The Committee recommended the addition of explanatory text to this effect to section 12 of the EML.

The Expert Committee also recommended the urgent updating of existing WHO guidance documents on

FDCs, as well as development of a guidance document outlining key criteria for differentiating the role and need for FDCs in different therapeutic indications (e.g. acute, chronic, communicable and noncommunicable diseases). This guidance should inform the selection and use of therapeutically appropriate, effective and safe FDCs that meet the needs of both patients and national public health systems.

Losartan – addition with square box – EML (ATC Code: C09CA01)

The Expert Committee noted that there is evidence of a favourable benefit–risk profile for the use of losartan for treatment of hypertension. The Committee therefore recommended the addition of losartan, with a square box as the representative of the pharmacological class of angiotensin-receptor blockers, to the EML for persons with hypertension, chronic heart failure with reduced ejection fraction, or chronic kidney disease who are unable to tolerate angiotensin-converting-enzyme inhibitors.

12.7: Fixed-dose combinations of cardiovascular medicines (new subsection)

Aspirin + atorvastatin + ramipril – rejected application for addition of fixed-dose combination – EML (ATC Code: C10BX06)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of the proposed fixed-dose combination formulation of aspirin + atorvastatin + ramipril to the core list of the EML. The Committee recognized that listing a single FDC of cardiovascular medicines would limit choice from the variety of combinations, components and dosages available that would be necessary to tailor therapy for individual patients but acknowledged that appropriate FDCs may offer some advantages over the single medicines given concomitantly in terms of adherence and reduced pill burden. The Committee recommended the addition of explanatory text to this effect to Section 12 of the EML.

The Expert Committee also recommended the urgent updating of existing WHO guidance documents on FDCs, as well as development of a guidance document outlining key criteria for differentiating the role and need for FDCs in different therapeutic indications (e.g. acute, chronic, communicable and noncommunicable diseases). This guidance should inform the selection and use of therapeutically appropriate, effective and safe FDCs that meet the needs of both patients and national public health systems.

Section 13: Dermatological medicines (topical)

No changes

Section 14: Diagnostic agents

No changes

Section 15: Disinfectants and antiseptics

15.1: Antiseptics

Hypochlorous acid – rejected application for addition of solution and hydrogel – EML and EMLc (ATC Code: D08AX07)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of hypochlorous acid solution and hydrogel to the EML and EMLc for use in wound management on the basis of inadequate evidence. The Committee noted that quality of evidence presented in the application for the solution was uncertain and that no evidence was presented for the hydrogel.

Section 16: Diuretics

No changes

Section 17: Gastrointestinal medicines

No changes

Section 18: Hormones, other endocrine medicines and contraceptives

18.3: Contraceptives

18.3.1: Oral hormonal contraceptives

Ulipristal acetate – addition for emergency contraception or contraceptive failure – EML (ATC Code: G03AD02)

The Expert Committee recommended the addition of ulipristal acetate to the core list of EML for emergency contraception within 5 days of unprotected sexual intercourse or contraceptive failure in women of reproductive age, on the basis of the evidence presented which supported UPA-EC as an effective and safe option for emergency contraception.

18.3.2: Injectable hormonal contraceptives

Medroxyprogesterone acetate – new formulation and strength, subcutaneous injection – EML (ATC Code: G03AC06)

The Expert Committee recommended the addition of the subcutaneous injection formulation of depot medroxyprogesterone acetate to the core list of the EML.

The Committee considered that the subcutaneous formulation, with appropriate training for administration, would provide an effective, safe and convenient contraceptive treatment choice. The possibility of self-administration may be an advantage in settings where availability of health-care

providers is limited.

The Committee also recommended the current listing of the intramuscular formulation be amended as proposed in the application, to clarify its route of administration.

18.5: Insulins and other medicines used for diabetes

SEE SEPARATE SUMMARY DOCUMENT ON DIABETES MEDICINES

Long-acting insulin analogues - rejected application for addition to EML and EMLc: Insulin glargine (ATC Code: A10AE04); Insulin detemir (ATC Code: A10AE05)

REJECTED APPLICATION: The Expert Committee noted that long-acting insulin analogues have been shown to be an effective treatment for type 1 diabetes in children, young people and adults.

However, the Committee noted that the magnitude of the benefit provided, compared with human insulin, was not large. The Committee considered that the benefits of insulin analogues over human insulin in terms of reduced glycated haemoglobin and reduced hypoglycaemia are modest and do not justify the current large difference in price between analogues and human insulin.

On the basis of this evaluation, the Expert Committee did not recommend the addition of long-acting insulin analogues as a pharmacological class to the core list of EML and EMLc for treatment of type 1 diabetes in adults, adolescents and children aged 2 years and above.

Second-line treatments for type 2 diabetes – comprehensive review - rejected application for addition – EML and EMLc

REJECTED APPLICATION: The Expert Committee acknowledged the wide coverage of the application, which compared all second-line therapies used in the intensification phase of therapy (i.e. between the initial therapy with metformin and any treatment combination containing insulin) in patients with type 2 diabetes.

The Committee noted that the application represents an advanced version of a report commissioned by the Canadian Agency for Drugs and Technologies in Health (CADTH). The Committee considered that data on the effectiveness of and harms caused by some of the medicines covered in the application will be supplemented in the coming years as new trials and longer follow-up are completed. The Committee considered the evidence provided was insufficient to propose changes to the EML, which thus far includes only sulfonylurea as intensification therapy.

The Committee confirmed the role of sulfonylureas as (one of) the most cost-effective treatment options for intensification therapy of type 2 diabetes.

The Committee noted that SGLT-2 inhibitors have been reported to be associated with a relevant clinical benefit as intensification therapy in patients at high risk of cardiovascular events, leading to a relevant reduction in overall mortality. This finding needs to be confirmed in other trials, before this class of medicines can be selectively supported for patients with type 2 diabetes.

On the basis of the evaluation, the Expert Committee did not recommend the inclusion of any additional

medicines for second-line therapy of type 2 diabetes.

Section 19: Immunologicals

No changes

Section 20: Muscle relaxants (peripherally-acting) and cholinesterase inhibitors

No changes

Section 21: Ophthalmological preparations

21.1: Anti-infective agents

Natamycin – addition – EML and EMLc (ATC Code: S10AA10)

Noting the overall favourable benefit–risk profile of topical natamycin for the treatment of fungal keratitis, the Expert Committee recommended the addition of natamycin ophthalmic suspension 5% to the core list of the EML and EMLc.

21.6: Anti-vascular endothelial growth factor (VEGF) preparations

Bevacizumab – rejected application for deletion – EML (ATC Code: L01XC07)

RETAIN IN EML: The Expert Committee did not recommend the deletion of bevacizumab for intravitreal administration for the treatment of neovascular age-related macular degeneration.

The Expert Committee noted that the reported cases of infection presented in the application were associated with sub-optimal compounding and administration practices. No additional clinical evidence relating to the overall benefit–harm ratio of intravitreal bevacizumab was provided.

The Committee reiterated the importance of compounding and administering intravitreal bevacizumab under sterile conditions.

Section 22: Oxytocics and antioxytocics

22.1: Oxytocics

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

RETAIN IN EML: The Expert Committee did not recommend the deletion of the listed indication of prevention of postpartum haemorrhage associated with misoprostol on the EML.

The Committee noted that very few new clinical data were included in the application and that the request was based on a reinterpretation of data previously presented.

The Expert Committee acknowledged that misoprostol is less effective than oxytocin infusion and is associated with adverse events (particularly vomiting and shivering). The circumstances of use have not changed; misoprostol remains an alternative for prevention of postpartum haemorrhage in resource-poor, community and rural settings where intravenous oxytocin is not available or cannot be safely administered. The additional two studies identified in this application provided no new evidence to support deletion. The Expert Committee noted that the WHO guidelines on postpartum haemorrhage were due to be updated in March 2017.

Section 23: Peritoneal dialysis solution

No changes

Section 24: Medicines for mental and behavioural disorders

No changes

Section 25: Medicines acting on the respiratory tract

25.1: Antiasthmatics and medicines for chronic obstructive pulmonary disease

Budesonide + formoterol – addition of combination inhaler (with square box indication) to EML but not EMLc (ATC Code: R03AK07)

The Expert Committee noted the evidence of greater benefit and the acceptable safety profile of the budesonide + formoterol combination inhaler.

The Expert Committee recommended the addition of budesonide + formoterol combination inhaler to the core list of EML (with a square box indication) as "single-inhaler therapy" for the management of asthma, in which a single inhaler can be used as regular therapy (maintenance therapy) to control the disease in patients who have failed first-line therapy.

The Expert Committee did not recommend the addition of budesonide + formoterol combination inhaler to the core list of the EMLc. The Committee noted concerns in relation to safety concerns with high doses of inhaled steroids in children.

The Committee noted the risks and safety concerns of the use of long-acting beta-2 agonist bronchodilators in rescue therapy and therefore did not recommend the use of budesonide + formoterol combination inhaler as rescue therapy, especially in children.

Section 26: Solutions correcting water, electrolyte and acid–base disturbances

26.3: Miscellaneous

Ready to use therapeutic food (RUTF) – rejected application for addition – EMLc (ATC Code: N/A)

REJECTED APPLICATION: The Expert Committee acknowledged the effectiveness of ready-to-use therapeutic food (RUTF) in the outpatient treatment of uncomplicated severe acute malnutrition in children aged 6–59 months and its alignment with WHO's 2013 *Guideline: updates on the management of severe acute malnutrition in infants and children*.

The Committee agreed that improving access to RUTF in health facilities at country level for the outpatient treatment of severe acute malnutrition is essential. However, the Committee considered that listing of RUTF on the EML may have implications for the availability of alternative products or formulations. In some countries and for some manufacturers, inclusion of RUTF in the EML may carry implications about the need to comply with requirements for pharmaceutical products and thus potentially have an impact on cost and access. The Expert Committee therefore did not recommend the addition of RUTF to the EMLc.

The Committee recommended further analysis of the implications and impacts of including RUTF in the EMLc and requested that the WHO Department of Nutrition for Health and Development be asked to prepare a report for the next Expert Committee meeting addressing the following aspects:

- country requirements if RUTF is included in the national EML (medicine/pharmaceutical vs food) and ability of local and international producers to comply with those requirements;
- cost and access implications if RUTF is listed as a medicine/pharmaceutical rather than a food;
- appropriate use of RUTF, i.e. only for uncomplicated cases of severe acute malnutrition and not for other children;
- progress by the CCNFSDU on the development of RUTF guidelines;
- outcome of ongoing systematic reviews of effectiveness and safety of RUTF.

Section 27: Vitamins and minerals

No changes

Section 28: Ear, nose and throat medicines

No changes

Section 29: Specific medicines for neonatal care

No changes

Section 30: Medicines for diseases of joints

No changes