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The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2017
(including the 20th WHO Model List of Essential Medicines
and the 6th Model List of Essential Medicines for Children)

World Health Organization

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Executive summary

The 21st meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Geneva, Switzerland, from 27 to 31 March 2017. The goal of the meeting was to review and update the 19th WHO Model List of Essential Medicines (EML) and the 5th WHO Model List of Essential Medicines for Children (EMLc).

The Expert Committee considered 92 applications, including proposals to add 41 new medicines and extend the indications for six existing listed medicines, five applications to delete medicines from the lists, and a comprehensive review of the antibacterials listed in sections 6.2.1 and 6.2.2 and their use in the treatment of 21 common, priority infectious syndromes, five paediatric infectious diseases and three sexually transmitted infections. In accordance with approved procedures[1], the Expert Committee evaluated the scientific evidence for the comparative effectiveness, safety and cost–effectiveness of the medicines. All changes to the lists are shown in Table 1. In summary, the Expert Committee:

- recommended the addition of 30 new medicines to the EML (17 to the core list and 13 to the Complementary List);
- recommended the addition of 25 new medicines to the EMLc (13 to the core list and 12 to the Complementary List);
- recommended the inclusion of additional indications for nine currently listed medicines; and
- rejected 20 applications for inclusion and/or deletion of medicines.

As part of the review of antibacterials, 10 additions were made to the EML and 12 to the EMLc, and a new categorization of antibacterials into three groups was proposed:

- *Access* – first- and second-choice antibiotics for the empirical treatment of most common infectious syndromes;
- *Watch* – antibiotics with higher resistance potential whose use as first- and second-choice treatment should be limited to a small number of syndromes or patient groups; and
- *Reserve* – antibiotics to be used mainly as “last-resort” treatment options.

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

Section 2.2 Opioid analgesics: The Expert Committee considered a review of methadone, fentanyl and tramadol for treatment of cancer pain. Accepting that there is a need for additional opioid treatment options for treatment of cancer pain, and noting that access to morphine is limited and that patients suffering from cancer often do not receive pain relief treatments, particularly in low- and middle-income countries, the Committee recommended the addition of transdermal fentanyl to the core list of the EML and the addition of a new indication for methadone for management

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

of cancer pain to the Complementary List of the EML and EMLc. The Expert Committee did not recommend the addition of tramadol, as the evidence reviewed showed it to be a suboptimal treatment for cancer pain compared with morphine and other strong opioids.

Section 6.2 Antibacterials: Section 6 of the EML covers anti-infective medicines. Disease-specific subsections within Section 6, such as those covering medicines for tuberculosis, HIV, hepatitis and malaria, have been regularly reviewed and updated, taking into consideration relevant WHO treatment guidelines. However, antibacterial medicines in sections 6.2.1 (Beta-lactam medicines) and 6.2.2 (Other antibacterials) had not been similarly reviewed and updated and so were the focus of a comprehensive review in 2017. This review addresses Objective 4 of WHO's Global Action Plan on Antimicrobial Resistance[2], which is to "optimize the use of antimicrobial medicines in human and animal health". Some antibacterials listed in sections 6.2.1 and 6.2.2 are also listed for the treatment of multidrug-resistant tuberculosis (MDR-TB). The impact of this review on antibacterials for treatment of tuberculosis was carefully considered, given the increasing problem represented by MDR-TB and the need to preserve effective treatments; however, the Committee made no changes to the antibiotics listed in section 6.4.2 Antituberculosis medicines as a result of the review.

After studying the proposals put forward for its consideration, the Expert Committee decided to consider only treatments for common infectious syndromes, excluding rare or hospital-acquired infections. The Committee then identified empirical treatment choices for common, community-acquired infections. These treatment choices are broadly applicable in most countries, using parsimony as a guiding principle. Alternatives for patients allergic to specific products were not considered. For each syndrome the Committee recommended first- and second-choice antibiotics, which are included on the Model Lists with the specific indication(s).

Taking account of the global recognition of the need for effective antimicrobial stewardship, as well as the need to ensure access to necessary antibiotics and appropriate prescribing, the Expert Committee also proposed that these antibiotics could be categorized in three groups – Access, Watch and Reserve. The Committee noted that the evidence base for assigning specific antibiotics and classes to the different groups was weak and the List will need further revision as new evidence accumulates. It was also clearly recognized that the general principles of Access/Watch/Reserve apply to many other antimicrobials, including antituberculosis medicines, antimalarials, antivirals and antifungals. The groups are described and defined in detail below.

[2] http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1

Access

The Access group includes antibiotics that are recommended as empirical first- or second-choice treatment options for common infectious syndromes and are listed in the EML/EMLc with the syndromes for which they are recommended. They should be widely available, at an affordable price, in appropriate formulations and of assured quality. First choices are usually narrow-spectrum agents with positive risk–benefit ratios and low resistance potential; second choices are generally broader-spectrum antibiotics with higher resistance potential or less favourable risk–benefit ratios. Where antibiotics in the Access group are recommended only for a limited number of indications and there are also concerns about existing or potential resistance, they may also be listed in the Watch group, and their use should be limited and monitored.

Access group antibiotics	
6.2.1 Beta-lactam medicines	**6.2.2 Other antibacterials**
amoxicillin	amikacin
amoxicillin + clavulanic acid	azithromycin*
ampicillin	chloramphenicol
benzathine benzylpenicillin	ciprofloxacin*
benzylpenicillin	clarithromycin*
cefalexin	clindamycin
cefazolin	doxycycline
cefixime*	gentamicin
cefotaxime*	metronidazole
ceftriaxone*	nitrofurantoin
cloxacillin	spectinomycin (EML only)
phenoxymethylpenicillin	sulfamethoxazole + trimethoprim
piperacillin + tazobactam*	vancomycin (oral)*
procaine benzyl penicillin	*vancomycin (parenteral)**
*meropenem**	

Italics = Complementary List.
*Watch group antibiotics included in the EML/EMLc only for specific, limited indications.

Watch

The Watch group includes antibiotic *classes* that are considered generally to have higher resistance potential and that are still recommended as first- or second-choice treatments but for a limited number of indications. These medicines should be prioritized as key targets of local and national stewardship programmes and monitoring. The group includes the highest priority agents on *the List of critically important antimicrobials for human medicine* (CIA)[3]. The CIA list ranks antimicrobials according to their relative importance in human medicine and can be used in the development of risk management strategies for the use of antimicrobials in food-production animals. Seven pharmacological classes were identified for this group. As noted above, monitoring systems should be in place to ensure that their use is in line with recommended indications.

Watch group antibiotics
Quinolones and fluoroquinolones e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
3rd-generation cephalosporins (with or without beta-lactamase inhibitor) e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime
Macrolides e.g. azithromycin, clarithromycin, erythromycin
Glycopeptides e.g. teicoplanin, vancomycin
Antipseudomonal penicillins with beta-lactamase inhibitor e.g. piperacillin + tazobactam
Carbapenems e.g. meropenem, imipenem + cilastatin
Penems e.g. faropenem

[3] http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1

Reserve

The Reserve group includes antibiotics that should be treated as "last-resort" options, or tailored to highly specific patients and settings, when other alternatives would be inadequate or had already failed (e.g. serious life-threatening infections due to multidrug-resistant bacteria). To preserve their effectiveness, these medicines should be protected and prioritized as key targets of high-intensity national and international stewardship programmes involving monitoring and utilization reporting. Eight antibiotics or antibiotic classes were identified for this group.

Reserve group ("last-resort") antibiotics
aztreonam
4th-generation cephalosporins, e.g. cefepime
5th-generation cephalosporins, e.g. ceftaroline
Polymyxins, e.g. polymyxin B, colistin
fosfomycin (IV)
Oxazolidinones, e.g. linezolid
tigecycline
daptomycin

The Expert Committee recommended the appointment of a standing EML working group to:

- consider reviewing additional clinical syndromes not included in the current update, e.g. medical and surgical prophylaxis, dental infections and acute undifferentiated fever;
- adapt the current clinical synopsis reviews with the aim of producing shorter structured documents;
- coordinate the development for the EML and EMLc of a guidance document on optimal dose and duration of antibiotic treatments to maximize clinical efficacy while minimizing the selection of resistance;
- review the differential effect of antibiotic classes on the selection of resistance;
- relate the work of the EML and EMLc to the future essential in vitro diagnostics list, which should include work on diagnostics related to antimicrobial resistance, as soon as feasible;
- propose improved methods for defining and communicating the key stewardship messages associated with the new categorization and develop more detailed guidance to assist with the implementation of recommendations in national programmes.

Section 6.2.4 Antituberculosis medicines: The Expert Committee recommended the listing of clofazimine for the new indication of multidrug-resistant tuberculosis (MDR-TB) on the Complementary List of the EML and EMLc. The Committee also recommended the addition of

delamanid to the Complementary List of the EMLc for the treatment of MDR-TB in children aged 6–17 years. Two paediatric fixed-dose combination formulations of isoniazid + pyrazinamide + rifampicin and of isoniazid + rifampicin were recommended for addition to the EMLc for treatment of tuberculosis. The Expert Committee did not recommend listing of gatifloxacin because it was not demonstrated to have a better benefit–harm ratio than currently listed alternatives. Ofloxacin (as an alternative to levofloxacin) was deleted in line with updated MDR-TB guidelines, and moxifloxacin, the other alternative to levofloxacin, became an independent listing. Streptomycin was deleted from the core list of the EML but is retained on the Complementary List of the EML and EMLc.

Section 6.4.2 Antiretrovirals: Noting the updated (2016) WHO Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, the Expert Committee recommended the addition of dolutegravir to the EML and of raltegravir to the EML and EMLc. The additional indication of pre-exposure prophylaxis (PrEP) for tenofovir disoproxil fumarate, alone or in combination with emtricitabine or lamivudine, was also recommended. The Expert Committee did not recommend the proposed antiretroviral formulations containing tenofovir alafenamide. The Committee recommended the deletion of 26 antiretroviral formulations/strengths, noting that they were no longer recommended by WHO guidelines.

Section 6.4.3 Other antivirals: The Expert Committee did not recommend the deletion of oseltamivir from the EML and EMLc, recognizing that it is the only medicine included on the Model Lists for critically ill patients with influenza and for influenza pandemic preparedness. However, the Committee noted that, since the inclusion of oseltamivir on the Model List in 2009, new evidence in seasonal and pandemic influenza has lowered earlier estimates of the magnitude of effect of oseltamivir on relevant clinical outcomes. The Committee recommended that the listing of oseltamivir be amended, moving the medicine from the core to the Complementary List, and that its use be restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients. The Expert Committee noted that WHO guidelines for pharmacological management of pandemic and seasonal influenza would be updated in 2017: unless new information is provided to support the use of oseltamivir in seasonal and pandemic outbreaks, the next Expert Committee might consider oseltamivir for deletion.

Section 8.2 Cytotoxic and adjuvant medicines: The Expert Committee recommended the addition of dasatinib and nilotinib to the Complementary List of the EML for the treatment of chronic myeloid leukaemia that is resistant to imatinib (i.e. second-line therapy). The Committee did not recommend listing other proposed cancer medicines: enzalutamide for metastatic prostate cancer; tyrosine kinase inhibitors (erlotinib, gefitinib and afatinib) and anaplastic lymphoma kinase (ALK) inhibitor (crizotinib) for non-small cell lung cancer; trastuzumab emtansine for metastatic breast cancer. The Committee considered that listing of these medicines was premature and recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of cancer medicines for the EML.

Section 10.1 Antianaemia medicines: The Expert Committee recommended the addition of erythropoiesis-stimulating agents as a pharmacological class, with a square box including

biosimilars, to the Complementary List of the EML and the EMLc for the treatment of anaemia in patients with chronic renal disease requiring dialysis.

Section 12 Cardiovascular medicines: The Expert Committee did not recommend the addition of two specific fixed-dose combinations (FDCs) of cardiovascular medicines for secondary prevention of cardiovascular events (aspirin + atorvastatin + ramipril) or hypertension (lisinopril + hydrochlorothiazide). However, the Committee considered that FDCs for non-communicable diseases may have advantages over single medicines given concomitantly, including improved adherence and reduced pill burden. The Committee considered that many different combinations of cardiovascular medicines exist, with multiple permutations of components from different therapeutic classes and varying strengths and dosages. The Committee recognized that listing a single FDC of cardiovascular medicines would limit choice from the variety of combinations, components and dosages available. The Committee recommended the addition of explanatory text to this effect to Section 12 of the EML, enabling discretion at country level in making choices for national EML selection.

Section 18 Hormones, other endocrine medicines and contraceptives: The Expert Committee did not recommend the inclusion of insulin analogues as a pharmacological class on the EML and EMLc, noting the small magnitude of benefit and current high price compared with human insulin.

The Expert Committee did not recommend inclusion of second-line medicines for type 2 diabetes on the EML. Of the second-line therapies considered, the Committee noted that sodium–glucose co-transporter 2 (SGLT-2) inhibitors have shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality, but that more data are needed to confirm this finding.

Two new contraceptive products were added to the EML: ulipristal acetate for emergency contraception and a new formulation of medroxyprogesterone acetate depot injection.

Other applications not recommended: In addition to those rejections noted above, the Expert Committee did not recommend the addition of ready-to-use therapeutic food or of hypochlorous acid solution. The Committee did not recommend the deletion of bevacizumab for ocular indications or of the indication of prevention of post-partum haemorrhage from the listing for misoprostol.

General issues: The Expert Committee recommended the formation of expert working groups to support future work for EML reviews and applications. Specifically, working groups were recommended for cancer medicines; to define criteria and thresholds for prioritization of medicines; antibiotics: to work on the implementation at country level of the proposed antibiotic categorization and to evaluate its adoption and potential hurdles; and for issues related to selective outcome reporting, publication bias, and open access to trial data, which can have relevant implications for the decision-making process.

The Committee expressed concerns about the high price of some medicines and supported the objectives of the upcoming Fair Pricing Forum as one initiative to increase awareness and participation of all relevant stakeholders. The issue of access to affordable essential medicines, notably those for cancer and diabetes, was discussed.

The Expert Committee supported the proposal for a WHO list of essential in vitro

diagnostics.

All applications and documents reviewed by the Expert Committee are available on the WHO website at: http://www.who.int/selection_medicines/committees/expert/21/en/.

Table 1
Summary of recommended changes to the EML and EMLc

EML – New medicines added		EMLc – New medicines added	
Medicine	**Indication**	**Medicine**	**Indication**
artesunate + pyronaridine	Malaria	artesunate + pyronaridine	Malaria
atazanavir + ritonavir	HIV	*aztreonam*	Reserve antibiotic
aztreonam	Reserve antibiotic	*Cephalosporins – 4th generation*	Reserve antibiotics
budesonide + formoterol	Asthma	*Cephalosporins – 5th generation*	Reserve antibiotics
Cephalosporins – 4th generation	Reserve antibiotics	cefixime	Antibiotic
Cephalosporins – 5th generation	Reserve antibiotics	clarithromycin	Antibiotic
daptomycin	Reserve antibiotic	*daptomycin*	Reserve antibiotic
dasatinib	Chronic myeloid leukaemia	*delamanid*	Tuberculosis
dihydroartemisinin + piperaquine	Malaria	dihydroartemisinin + piperaquine	Malaria
dolutegravir	HIV	*Erythropoiesis-stimulating agents*	Anaemia of chronic renal disease
efavirenz + lamivudine + tenofovir DF	HIV	*fosfomycin (IV)*	Reserve antibiotic
Erythropoiesis-stimulating agents	Anaemia of chronic renal disease	isoniazid + pyrazinamide + rifampicin	Tuberculosis
fentanyl	Cancer pain	isoniazid + rifampicin	Tuberculosis
fosfomycin (IV)	Reserve antibiotic	isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	HIV
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	HIV	itraconazole	Fungal infection

Table 1 *continued*

EML – New medicines added		EMLc – New medicines added	
Medicine	**Indication**	**Medicine**	**Indication**
itraconazole	Fungal infection	lamotrigine	Epilepsy
lamotrigine	Epilepsy	*methadone*	Cancer pain
losartan	Hypertension	*meropenem*	Antibiotic
meropenem	Antibiotic	natamycin	Fungal infection
natamycin	Fungal infection	*Oxazolidinones*	Reserve antibiotics
nilotinib	Chronic myeloid leukaemia	piperacillin + tazobactam	Antibiotic
Oxazolidinones	Reserve antibiotics	*Polymyxins*	Reserve antibiotics
piperacillin + tazobactam	Antibiotic	raltegravir	HIV
Polymyxins	Reserve antibiotics	*tigecycline*	Reserve antibiotic
raltegravir	HIV	voriconazole	Fungal infection
sofosbuvir + velpatasvir	Hepatitis C		
tigecycline	Reserve antibiotic		
ulipristal	Emergency contraception		
voriconazole	Fungal infection		
zoledronic acid	Bone metastases		

EML – New/changed indications		**EMLc – New/changed indications**	
Medicine	**Indication**	**Medicine**	**Indication**
amikacin	Antibiotic	amikacin	Antibiotic
azithromycin	Yaws	azithromycin	Yaws
clofazimine	Tuberculosis	*clofazimine*	Tuberculosis
emtricitabine + tenofovir DF	HIV PrEP	ivermectin	Anthelminthic
ivermectin	Anthelminthic	*methadone*	Cancer pain
methadone	Cancer pain	*oseltamivir*	Influenza
oseltamivir	Influenza	oxygen	Hypoxaemia
oxygen	Hypoxaemia		
tenofovir DF	HIV PrEP		

Table 1 *continued*

EML – New formulations		EMLc – New formulations	
Medicine	**Formulation**	**Medicine**	**Formulation**
abacavir + lamivudine	Tablet (dispersible, scored): 120 mg + 60 mg	abacavir	Tablet (dispersible, scored): 60 mg
amoxicillin	Powder for injection: 250 mg; 500 mg; 1 g	abacavir + lamivudine	Tablet (dispersible, scored): 120 mg + 60 mg
amoxicillin + clavulanic acid	Powder for injection: 500 mg + 100 mg; 1000 mg + 200 mg	amoxicillin	Powder for injection: 250 mg; 500 mg; 1 g
doxycycline	Powder for injection: 100 mg	amoxicillin + clavulanic acid	Powder for injection: 500 mg + 100 mg; 1000 mg + 200 mg
medroxyprogesterone acetate	Injection (SC): 104 mg/0.65mL	artesunate	Rectal dosage form: 100 mg
paracetamol	Oral liquid: 120 mg/5 mL	doxycycline	Powder for injection: 100 mg
vancomycin	Capsule: 125 mg; 250 mg	erythromycin	Eye ointment: 0.5%
		lopinavir + ritonavir	Capsule with oral pellets: 40 mg + 10 mg
		paracetamol	Oral liquid: 120 mg/5 mL
		vancomycin	Capsule: 125 mg; 250 mg
		zidovudine	Tablet (dispersible, scored): 60 mg

Table 1 *continued*

EML – Medicines/formulations deleted		EMLc – Medicines/formulations deleted	
Medicine	**Formulation**	**Medicine**	**Formulation**
abacavir	Oral liquid: 100 mg/5 mL	abacavir	Oral liquid: 100 mg/5 mL
atazanavir	Solid oral dose form: 150 mg	atazanavir	Solid oral dose form: 150 mg
efavirenz	Capsule: 50 mg; 100 mg; 200 mg	efavirenz	Capsule: 50 mg; 100 mg; 200 mg
lamivudine	Oral liquid: 50 mg/mL	lamivudine + nevirapine + stavudine	Tablet (dispersible): 30 mg + 50 mg + 6 mg
lamivudine + nevirapine + stavudine	Tablet: 150 mg + 200 mg + 30 mg Tablet (dispersible): 30 mg + 50 mg + 6 mg Tablet: 200 mg		
ofloxacin	For MDR-TB as an alternative to levofloxacin	*ofloxacin*	For MDR-TB as an alternative to levofloxacin
saquinavir	All dose forms/ strengths	stavudine	All dose forms/ strengths
stavudine	All dose forms/ strengths	zidovudine	Capsule: 100 mg
streptomycin (core list)	Powder for injection: 1 g		
zidovudine	Capsule: 100 mg		

List of participants

Committee members

Zeba Aziz, Professor of Oncology and Haematology/Consultant Oncologist & Haematologist, Hameed Latif Hospital, Lahore, Pakistan

Lisa Bero, Chair of Medicines Use and Health Outcomes, Charles Perkins Centre, University of Sydney, Sydney, Australia (*Chair*)

Franco Cavalli, Scientific Director, Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland

Graham Cooke, Clinical Senior Lecturer in Infectious Diseases, Department of Medicine, Imperial College, London, England (*Vice-Chair*)

Facundo Garcia-Bournissen, Associate Researcher, Argentine National Science and Technology Research Council (Consejo Nacional de Investigaciones Cientificas y Tecnicas – CONICET) and Paediatric Clinical Pharmacologist, Buenos Aires Children´s Hospital, Buenos Aires. Argentina

Mohammed Hassar, Internist and Clinical Pharmacologist, Rabat School of Medicine and Pharmacy, Rabat, Morocco

Gregory Kearns, President, Arkansas Children's Research Institute, and Senior Vice President and Chief Research Officer, Arkansas Children's Hospital, Little Rock, AR, USA

Robert Mvungi, Cardiologist, Department of Cardiovascular Medicine, Muhimbili National Hospital, Dar es Salaam, United Republic of Tanzania

Francis Ofei, Associate Professor of Endocrinology, University of Cape Coast, School of Medical Sciences, Cape Coast, Ghana

Gabriela Prutsky Lopez, Pediatric Hospitalist, Boston Children's Hospital, Boston, MA, USA, and Lead Investigator and Founder, Unidad de Conocimiento y Evidencia (CONEVID), Cayetano Heredia University, Lima, Peru

Celine Pulcini, Infectious and Tropical Diseases Department, University Hospital of Nancy, Nancy, France

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

Fatima Suleman, Associate Professor, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa (*Rapporteur*)

Worasuda Yoongthong, Chief of National Drug Policy Division, Bureau of Drug Control, Food and Drug Administration of Thailand, Nonthaburi, Thailand

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

Temporary advisers

Sumanth Gandra, Resident Scholar, Centre for Disease Dynamics, Economics and Policy, New Delhi, India.

Stephan Harbarth, Department of Internal Medicine Specialties, Division of Infectious Diseases, Hôpitaux universitaires de Genève, Geneva, Switzerland.

Mike Sharland, Professor of Paediatric Infectious Diseases, St George's University Hospitals NHS Foundation Trust, London, England

Representatives of other organizations

United Nations Population Fund (UNFPA)

Wilma Doedens, UNFPA Office in Geneva, Switzerland

Petra ten Hoope-Bender, UNFPA Office in Geneva, Switzerland

United Nations Children's Fund (UNICEF)

Henrik Nielsen, Technical Specialist, Essential Medicines Unit, Medicines and Nutrition Centre, UNICEF Supply Division, Copenhagen, Denmark

WHO Regional Offices

Jose Luis Castro, Advisor, Rational Use of Medicines, WHO Regional Office for the Americas/Pan American Health Organization, Washington, DC, USA

Alexandra Guta, Specialist in Medicines and Technologies, WHO Regional Office for the Americas/Pan American Health Organization, Washington, DC, USA

Hanne Bak Pedersen, Programme Manager, Health Technologies and Pharmaceuticals, WHO Regional Office for Europe, Copenhagen, Denmark

Jane Robertson, Technical Officer, Health Technologies and Pharmaceuticals, WHO Regional Office for Europe, Copenhagen, Denmark

Observer

Peter Collignon, Department of Microbiology and Infectious Diseases, Canberra Hospital, Canberra ACT, Australia

WHO Secretariat (WHO headquarters, Geneva, Switzerland)

Suzanne Hill, Director, Department of Essential Medicines and Health Products, Health Systems and Innovation Cluster

Gilles Forte, Coordinator, Office of the Director, Department of Essential Medicines and Health Products

Nicola Magrini, Scientist, Secretary of the Expert Committee on Selection and Use of Essential Medicines; Innovation, Access and Use, Department of Essential Medicines and Health Products

Lorenzo Moja, Technical Officer, Secretariat of the Expert Committee on Selection and Use of Essential Medicines; Innovation, Access and Use, Department of Essential Medicines and Health Products

Bernadette Cappello, Technical Officer, Secretariat of the Expert Committee on Selection and Use of Essential Medicines; Innovation, Access and Use, Department of Essential Medicines and Health Products

Carmem Pessoa da Silva, Medical Officer, Antimicrobial Resistance, Office of the Director-General

Elizabeth Tayler, Technical Officer, Antimicrobial Resistance, Office of the Director-General

Filiberto Beltran Velazquez, Technical Officer, Evidence and Programme Guidance, Department of Nutrition for Health and Development

Declaration of interests

Declarations of interests of Expert Committee Members, Temporary Advisers and WHO Secretariat

Management of conflicts of interest was a key priority throughout the process of development of recommendations. In reviewing and assessing the declarations of interest of the members of the 21st Expert Committee on the Selection and Use of Essential Medicines, the WHO Department of Essential Medicines and Health Products sought the advice of the Office of Compliance, Risk Management and Ethics.

More than 90 applications for addition, deletion or changes to medicines on the Model Lists were considered by the 21st Expert Committee on the Selection and Use of Essential Medicines. The full list of applications is available on the WHO website.

Before the meeting, all members of the Expert Committee, together with temporary advisers, submitted written disclosures of relevant competing interests for consideration before being confirmed as participants in the said meeting. Possible conflicting interests included employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry-sponsored grants including contracted research, patents received or pending, royalties, stock ownership or options, other personal financial interests, and whether there is a financial relationship between the institution or employer and a commercial entity that has an interest in medicines evaluated by the Expert Committee.

Committee members and temporary advisers were also asked to disclose academic or scientific activities, including leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about a medicine. In addition, all members were asked at the start of the meeting to update their declarations if any new conflicts had arisen in the meantime.

Members and temporary advisers who declared having no financial conflicts of interests were: Zeba Aziz, Lisa Bero, Sumanth Gandra, Facundo Garcia-Bournissen, Mohammed Hassar, Robert Mvungi, Francis Ofei, Gabriela Prutsky-Lopez, Shalini Sri Ranganathan, Fatima Suleman, Worasuda Yoongthong and Mei Zeng.

Lisa Bero is Co-Chair of the Cochrane Collaboration Governing Board. Cochrane is a global non-profit organization that consists of an independent network of researchers producing high-quality systematic reviews of evidence for health-care interventions. She has authored studies about reporting biases and promotion of gabapentin and an editorial on bevacizumab; both medicines were under evaluation at this meeting.

Franco Cavalli declared that his institution (Ente Ospedaliero Cantonale, Switzerland) has received funding from Mundipharma for testing a medicine in testicular lymphoma, a disease not under evaluation at this meeting. He also declared that he is the organizer of the International Conference on Malignant Lymphoma and coordinator of the World Oncology Forum, activities for which he is unpaid.

Graham Cooke declared that his institution (Imperial College London, England) is involved in multicentre trials as one site of patient recruitment to test the efficacy and safety of medicines on hepatitis C. Oral agents are produced by the pharmaceutical companies Bristol-Myers Squibb, Gilead and Janssen. Dr Cooke declared that he chairs the Lancet Commission on

Hepatitis C, for which he is unpaid.

Stephan Harbarth leads the WHO Collaborating Centre on Patient Safety Infection Control Programme. He declared that his institution (University of Geneva Hospitals, Switzerland) has received funding from Pfizer for designing and conducting a study on antimicrobial resistance burden in several countries. He also declared that his institution has received funding from the Innovative Medicines Initiative, a joint undertaking between the European Union and the European Pharmaceutical Industry Association, to lead a work package of the DRIVE-AB (Driving reinvestment in research and development and responsible antibiotic use) Project. These projects are not related to antibiotics evaluated at this meeting.

Gregory Kearns declared having received honoraria from Janssen Pharmaceuticals and from Roche to provide expert advice on the design and conduct of pharmacokinetics studies.

Gabriela Prutsky-Lopez declared being an unpaid member of the Expert Committee for the Selection and Inclusion of Medicines in the Strategic Fund of the Pan American Health Organization (PAHO).

Celine Pulcini declared that her institution (University of Lorraine, Nancy, France) has received funding from the Innovative Medicines Initiative, a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), to participate in the DRIVE-AB Project (Workpackage 1a). This project is not related to antibiotics evaluated at this meeting.

Mike Sharland chairs the Department of Health's Expert Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI). His institution (St George's University Hospitals, London, England) is involved in multicentre trials as one site to test the efficacy of vaccines and antibiotics in children and receives institutional funding from Ablynx, Alios, Cubist, Cempra, GSK, Janssen, Medimmune, Novartis, Novovax, Pfizer and Regeneron.

After analysing each declaration, the Secretariat of the EML, assisted by the Office of Compliance, Risk Management and Ethics, concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the Expert Committee process. Conflicts of interests declared by Gregory Kearns were considered minor. No other member had personal financial or commercial interests related to medicines under evaluation. Institutional grants and funding were not considered as creating the potential for inappropriate influence over the Expert Committee members and temporary advisers. Options for conditional participation, partial or total exclusion of any expert were therefore not discussed.

Declarations of interest for the WHO Secretariat

Declarations of interest of the WHO Secretariat were also reviewed (although this was not mandatory) and guidance was sought from the Office of Compliance, Risk Management and Ethics with respect to potential conflicts.

Bernadette Cappello, Gilles Forte, Suzanne Hill, Nicola Magrini and Lorenzo Moja had no financial conflicts of interests.

Lorenzo Moja authored one systematic review on safety of a medicine under evaluation (bevacizumab).

In 2014, Nicola Magrini was called to testify by the Italian Antitrust Authority in a case against Roche and Novartis for anticompetitive activities in respect of one medicine under evaluation (bevacizumab). While it was determined that he had no direct conflict of interest with

respect to the evaluation of bevacizumab, he was advised that he might consider voluntarily recusing himself from that evaluation to avoid a perceived conflict of interest. He did decide to recuse himself from participating in the discussions and formulation of the recommendation on bevacizumab.

1. Introduction

The 21st meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines was held from 27 to 31 March 2017 in Geneva, Switzerland.

The meeting was opened on behalf of the Director-General of WHO by Suzanne Hill, Director, Department of Essential Medicines and Health Products. Dr Hill welcomed Committee members and temporary advisers, representatives from WHO regional offices and from nongovernmental organizations, and other participants on behalf of the Director-General.

The large number of applications received for consideration by the Expert Committee was highlighted, and the comprehensive reviews of antibacterial medicines and medicines for treatment of diabetes were noted particularly. Dr Hill acknowledged the work already undertaken by committee members and temporary advisers in reviewing the applications and thanked these participants for their preparation and valued contribution.

2. Open session

The open session of the meeting was chaired by Suzanne Hill, Director, Essential Medicines and Health Products, on behalf of the Director-General, and was attended by a variety of interested parties, representatives of nongovernmental organizations and representatives of WHO Member States.

Dr Hill introduced Marie-Paule Kieny, Assistant Director-General, Health Systems and Innovations, who addressed the Open Session on behalf of WHO Director-General, Dr Margaret Chan.

Dr Kieny acknowledged the upcoming 40th anniversary of the Essential Medicines List (EML) later in 2017 and recognized the Model List as one of the flagship products of WHO. She summarized some of the historical achievements over 40 years of the EML and outlined its evolution over time, stressing the importance of transparency and rigorous evaluation of evidence in support both of the efficacy estimates of medicines and of their risk–benefit ratios.

Dr Kieny noted some of the important decisions facing the Expert Committee and reminded Committee members and temporary advisers of their responsibility to provide advice to WHO in their individual capacities as experts – not as representatives of their governments or organizations – and to prepare and approve a report of the meeting at the end of proceedings.

A full transcript of Dr Kieny's address is available on the WHO website at http://www.who.int/selection_medicines/committees/expert/21/KIENY_Opening_Remarks_OpenSession27March.pdf?ua=1.

Presentations were made by members of the WHO Secretariat:

- Peter Beyer, Senior Adviser, Innovation, Access and Use: Global development and stewardship framework for antimicrobial resistance.
- Nicola Magrini, Secretary of the Expert Committee: the WHO Essential Medicines List at 40.
- Francis Moussy, Technical Officer, Innovation, Access and Use: Proposal for a WHO Model List of Essential In Vitro Diagnostics.

Presentations and/or statements of relevance to the agenda of the Expert Committee were made by the following participants:

- Myriam Henkens, Médecins Sans Frontières, Paris, France
- Brendan Shaw, International Federation of Pharmaceutical Manufacturers & Associations, Geneva, Switzerland
- Esteban Burrone, Medicines Patent Pool, Geneva, Switzerland
- Thirukumaran Balasubramanian, Knowledge Ecology International, Geneva, Switzerland
- Margaret Ewen, Health Action International, Amsterdam, Netherlands
- Manica Balasegaram, Drugs for Neglected Diseases Initiative, Global Antibiotic

Research and Development Partnership, Geneva, Switzerland

Copies of the presentations and statements are available on the WHO website at http://www.who.int/selection_medicines/committees/expert/21/en/.

3. General items

3.1: Alignment of the Essential Medicines List and WHO guidelines

With the introduction of GRADE methodology (grading of recommendations, assessment, development and evaluation) to develop WHO guidelines and a more transparent and homogenous internal process (through the WHO Guideline Review Committee, responsible for reviewing guideline protocols, drafts and final reporting), there have been important improvements in evidence synthesis and guideline reporting.

In some therapeutic areas (HIV, hepatitis B and C, tuberculosis, malaria, some priority neglected tropical diseases, contraception and family planning, sexually transmitted infections), WHO guidelines are frequently and regularly updated with the use of systematic reviews and/or network meta-analyses that form the basis for an optimal decision-making process as well as for informing decisions regarding medicines for inclusion on the EML. When these high-quality evidence summaries are available, they are shared between the EML Secretariat and the guideline development group to improve consistency and alignment. Timing of publication of both WHO guidelines and EML has also been coordinated to minimize unintended delays.

3.2: New format for the Technical Report

To help ensure that the EML Technical Report represents the best evidence currently available and can therefore better inform country policies, the format of each medicines chapter or section has been revised. The new format that has been developed offers has several advantages, making it easier for health professionals and policy-makers to identify basic information such as the ATC code or key findings such as the magnitude of benefits and harms associated with any particular medicine and additional evidence (not in the application) considered by the Expert Committee. The 2017 report uses the new format and sets the stage for future developments in presenting summaries of evidence on essential medicines. As the number of medicines evaluated at each Expert Committee meeting continues to rise steadily, the structured format will allow more rapid retrieval of the relevant information by the Expert Committee during the decision-making process and by readers. There is also growing awareness that, to understand key findings on medicines and to facilitate judgements on the public health relevance of an application, health professionals and policy-makers need succinct, structured and uniform summaries. An increasing number of applications involved comprehensive reviews of available treatments for diseases/syndromes rather than being concerned with individual medicines; examples are antibiotic and diabetes medicines reviews at the 2017 meeting and cancer medicines, as a continuation of work started at the 2015 meeting. The new format of the present report allows comparative evaluation of all available therapeutic options for target diseases or specific indications, facilitating broader comparisons and more selective listing.

3.3: Increasing the affordability of high-priced medicines

The issue of affordability of a number of high-priced medicines, specifically those for cancer, hepatitis C and diabetes, was raised. The Committee has added high-priced medicines, such as those for hepatitis C and cancer, to the EML and/or EMLc as an important step in making them more affordable and more widely accessible. The Committee highlighted the need for continuing assessment, at country level, of pricing mechanisms for, availability of and access to high-priced medicines that are added to the EML and/or EMLc.

3.4: EML Working Groups and comprehensive reviews

The Expert Committee recommended the establishment of three standing Working Groups to prepare the work for the next Expert Committee, which will meet in 2019, in complex therapeutic areas such as antibiotics and cancer and to support a WHO policy on transparency and timely public disclosure of clinical trial results.

An EML Antibiotics Working Group should be established to continue the work that started with the 2017 comprehensive review of the antibiotic section and to prepare the work of the next Expert Committee. Specifically, the Committee recommended review of additional infectious disease syndromes, including typhoid fever, medical and surgical infection prophylaxis, dental infections and acute undifferentiated fever. The EML Antibiotics Working Group could revise and consolidate the newly proposed categorization of antibiotics ("Access", "Watch" and "Reserve" groups), assessing whether this tool can assist in activities such as local, national and global monitoring of antibiotic use, development of guidelines and educational activities to improve antibiotic use. The existing listings and groupings may well change over time, with the aim of balancing the objectives of preserving antibiotic effectiveness while guaranteeing necessary access.

The Expert Committee recommended the appointment of a Cancer Working Group to review selected oncology medicines for the EML and EMLc. The aim would be greater clarity on the principles that guide the selection of optimal medicines to be considered for EML inclusion and review of available tools and thresholds for clinical and public health relevance of a medicine. Improved application quality is also needed, together with more comprehensive comparative evaluations that are not restricted to single medicines. For some cancers, there is a need to review the necessary associated diagnostic capacity in order to appropriately select patients suitable for treatment. The Cancer Working Group should consider other important conditions for review that were not part of the previous update, including (but not limited to) multiple myeloma and renal and brain cancers.

Finally, the Committee recognized the impact that selective reporting and publication bias can have on the availability of data in support of applications for the inclusion of medicines on the EML and EMLc, as highlighted by the applications for oseltamivir and gabapentin considered at this meeting. The Committee also recognized the high prevalence of both study and outcome reporting biases. It proposed the establishment of a Working Group to address the issues of selective outcome reporting, publication bias, and open access to clinical trials results in relation to applications for the EML and EMLc. The Working Group should work closely with the Department of Information, Evidence and Research on full and timely public disclosure of results from clinical trials.

3.5: Proposal for a WHO list of essential in vitro diagnostics

The recommendations and comments of the Expert Committee in relation to a proposed WHO list of essential in vitro diagnostics were as follows:

- The Committee acknowledged that specific tests are essential to diagnose the disease or identify the subpopulation for which certain medicines may be indicated, and to monitor the effectiveness or toxicity of medications. Moreover, diagnosis often has important implications for prognosis.
- The Committee recognized that countries might seek advice about the technologies to prioritize, how to shift from one technology to another, and which technologies should accompany essential medicines since they are strongly interconnected.
- The Committee recognized that the idea of a model list of essential in vitro diagnostics, developed and maintained by WHO, merits exploration, basing its process, methodology and transparency on the Model List of Essential Medicines.
- The diagnostics list may initially focus on in vitro diagnostics.
- The initial proposed priority areas (tuberculosis, malaria, HIV, and hepatitis B and C) may be appropriate for the first iteration of the list but the scope should extend to other areas, including other antimicrobials and noncommunicable diseases, as soon as possible.
- The Committee recommended that strong links should be maintained between the planned Strategic Advisory Group of Experts on In Vitro Diagnostics, which will oversee the diagnostics list, and the Expert Committee on Selection and Use of Essential Medicines.
- The diagnostics list should be integral to the development of both medical guidelines and laboratory accreditation schemes.

4. Summary of recommendations

Additions to Model Lists

Section 2.2: Fentanyl transdermal patches were added to the core list of the EML for the management of cancer pain. Methadone was added to the Complementary List of the EMLc for the same indication.

Section 5: Lamotrigine was added to the core list of the EML and EMLc as adjunctive therapy for treatment-resistant partial or generalized epileptic seizures.

Sections 6.2.1 and 6.2.2: Piperacillin + tazobactam and meropenem were added to the core list of the EML and EMLc. Cefixime and clarithromycin were added to the core list of the EMLc. The following antibiotics and antibiotic classes were added to the Complementary List of the EML and EMLc as Reserve group medicines: aztreonam, 4th-generation cephalosporins, 5th-generation cephalosporins, daptomycin, fosfomycin (IV), oxazolidinones, polymyxins and tigecycline.

Section 6.2.4: Delamanid was added to the Complementary List of the EMLc as a reserve second-line medicine for treatment of multidrug-resistant tuberculosis (MDR-TB) in children aged 6 years and above. Paediatric fixed-dose combination formulations of isoniazid + pyrazinamide + rifampicin and isoniazid + rifampicin for tuberculosis were added to the core list of the EMLc.

Section 6.3: Itraconazole and voriconazole were added to the core list of the EML and EMLc for treatment and prophylaxis of various invasive fungal infections.

Section 6.4.2: For treatment of HIV infection, fixed-dose combinations of atazanavir + ritonavir and efavirenz + lamivudine + tenofovir disoproxil fumarate were added to the EML. Dolutegravir and raltegravir were added to the EML in a new subsection (6.4.2.4 Integrase inhibitors). Raltegravir was also added to the EMLc. A fixed-dose combination of isoniazid + pyridoxine + sulfamethoxazole + trimethoprim was added to the EML and EMLc in a new subsection (6.4.2.5 Medicines for prevention of HIV-related opportunistic infections).

Section 6.4.4: Sofosbuvir + velpatasvir was added to the core list of the EML for the treatment of chronic hepatitis C, genotypes 1 to 6. This product is the first pan-genotypic combination for treatment of hepatitis C.

Section 6.5.3: Two new fixed-dose combinations for curative treatment of malaria were added to the core list of the EML and EMLc: artesunate + pyronaridine and dihydroartemisinin + piperaquine.

Section 8.2: Nilotinib and dasatinib were added to the Complementary List of the EML for treatment of imatinib-resistant chronic myeloid leukaemia. Zoledronic acid was added to the Complementary List of the EML for treatment of malignancy-related bone disease.

Section 10.1: Erythropoiesis-stimulating agents as a class were added to the Complementary List of the EML and EMLc for treatment of anaemia in patients with chronic kidney disease on

dialysis. The square box listing includes epoetin (alfa, beta, theta), darbepoetin alfa, methoxy polyethylene glycol-epoetin beta (EML) and epoetin (alfa, beta, theta), darbepoetin alfa (EMLc) and their respective biosimilars.

Section 12: Losartan, with a square box as representative of the pharmacological class of angiotensin receptor blockers, was added to the core list of the EML for management of hypertension, heart failure or chronic kidney disease in patients unable to tolerate angiotensin-converting enzyme inhibitors.

Section 18: Ulipristal acetate was added to the core list of the EML for use as emergency contraception within 5 days of unprotected sexual intercourse or contraceptive failure.

Section 21: Natamycin eye drops were added to the core list of the EML and EMLc for treatment of fungal keratitis.

Section 25.1: Budesonide + formoterol, with a square box as representative of the pharmacological classes of inhaled corticosteroids (ICS) and long-acting beta-agonists, was added to the core list of the EML as regular maintenance therapy for the management of asthma. The product was not added to the EMLc because of safety concerns about high doses of ICS in children.

Deletions from Model Lists

Section 6.2.4: Ofloxacin, as an alternative to levofloxacin for multidrug-resistant tuberculosis, was deleted from the EML and EMLc. Streptomycin was removed from the core list of the EML as a first-line tuberculosis treatment.

Section 6.4.2: Formulations and strengths of the following antiretroviral medicines were deleted from the EML: abacavir, atazanavir, efavirenz, lamivudine, lamivudine + nevirapine + stavudine, saquinavir, stavudine and zidovudine. Formulations and strengths of the following antiretroviral medicines were deleted from the EMLc: abacavir, atazanavir, efavirenz, lamivudine + nevirapine + stavudine, nevirapine, stavudine and zidovudine.

Changes to listings

Section 6.4.3: The listing of oseltamivir on the EML and EMLc was moved from the core to the Complementary List and restricted to use in severe illness due to confirmed or suspected influenza infection in critically ill hospitalized patients.

New indications

Section 1.4 (new section): The indications for oxygen on the core list of the EML and EMLc were extended to include management of hypoxaemia in addition to the current listing as an inhalational medicine in general anaesthesia. The new indication is recommended in a new section (1.4 Medical gases). The title of Section 1 was changed to “Anaesthetics, preoperative

medicines and medical gases".

Section 2.2: An additional indication for methadone for use in the management of cancer pain was added to the Complementary List of the EML.

Section 6.1: An additional indication for ivermectin for use as an intestinal anthelminthic was added to the core list of the EML and EMLc.

Section 6.2.2: Amikacin was included in the core list of the EML and EMLc, in addition to its current listing in section 6.2.4 as an antituberculosis medicine. A new indication as treatment for yaws was included for azithromycin in the EML and EMLc.

Section 6.2.4: Clofazimine was included in the Complementary List of the EML and EMLc for an additional indication as a reserve second-line medicine for treatment of multidrug-resistant tuberculosis.

Section 6.4.2: The additional indication for pre-exposure prophylaxis of HIV infection was included for tenofovir disoproxil fumarate, alone and in combination with emtricitabine, on the core list of the EML.

New dosage form and/or strength

Section 2.1: A new strength of paracetamol oral liquid (120 mg/5 mL) was added to the core list of the EML and EMLc. It was also added to Section 7.1 (Antimigraine medicines).

Sections 6.2.1 and 6.2.2: Parenteral formulations of amoxicillin, amoxicillin + clavulanic acid, and doxycycline and of oral vancomycin were added to the EML and EMLc.

Section 6.4.2: A new strength of abacavir + lamivudine was added to the core list of the EML and EMLc. New formulations/strengths of abacavir, lopinavir + ritonavir, and zidovudine were added to the EMLc.

Section 6.5: A new strength of artesunate rectal dose form (100 mg) was added to the EMLc for pre-referral treatment of severe malaria.

Section 18: A new strength and formulation of medroxyprogesterone acetate was added to the EML as an injectable hormonal contraceptive.

Section 21: Erythromycin eye ointment was added to the core list of the EMLc for ocular treatment of infections due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae* in neonates.

Rejected applications

Section 2.2: The application for addition of tramadol to the EML and EMLc for the management of cancer pain was not recommended on the basis of tramadol being a suboptimal cancer pain treatment compared with morphine and other strong opioids.

Section 5: The application for addition of gabapentin to the EML for the management of neuropathic pain was not recommended on the basis of uncertainty in reported efficacy estimates related to publication and outcome reporting biases in the available evidence.

Section 6.2.4: The application for addition of gatifloxacin as a reserve second-line drug for multidrug-resistant tuberculosis was not recommended, as the available evidence did not show it to have a superior benefit–harm ratio compared with alternative fluoroquinolones included on the list.

Section 6.4.2: Three applications seeking listing of fixed-dose combinations including tenofovir alafenamide for treatment of HIV were not recommended because of limited evidence of a relevant clinical advantage over currently listed combinations.

Section 6.4.3: The application proposing deletion of oseltamivir from the EML and EMLc was not recommended, although changes to the current listing of oseltamivir were recommended (see "Changes to listings", above).

Section 6.4.4: The application for addition of tenofovir alafenamide to the core list of the EML for treatment of chronic hepatitis B was not recommended because of limited evidence of a relevant clinical advantage over tenofovir disoproxil fumarate. The application for addition of elbasvir + grazoprevir to the core list of the EML for treatment of chronic hepatitis C was not recommended as the pan-genotypic combination of sofosbuvir + velpatasvir was preferred.

Sections 8.2 and 8.3: Applications requesting listing for erlotinib, gefitinib, afatinib and crizotinib for treatment of non-small cell lung cancer; trastuzumab emtansine for metastatic breast cancer and enzalutamide for metastatic prostate cancer were not recommended. Establishment of a cancer medicines working group to inform and support future applications for cancer medicines on the Model Lists was recommended.

Section 12: Applications requesting listing for fixed-dose combinations (FDCs) of lisinopril + hydrochlorothiazide for hypertension not adequately controlled with monotherapy, and aspirin + atorvastatin + ramipril for secondary prevention of cardiovascular disease were not recommended. Listing of a particular FDC would limit choice from the variety of combinations, components and dosages required to appropriately tailor therapy. Explanatory text was added to this section of the list, recognizing the potential value of FDCs of currently listed essential medicines in improving adherence and reducing pill burden. Countries should use their discretion at national level regarding FDC choices.

Section 15: The application requesting addition of hypochlorous acid solution and hydrogel to the EML and EMLc for use as a wound disinfectant and in wound management was not recommended because of low-quality or inadequate evidence.

Section 18.5: The application requesting addition of insulin analogues to the EML and EMLc for treatment of type 1 diabetes was not recommended because higher costs outweigh potential benefits compared with human insulin. The application proposing addition of various second-line treatments for type 2 diabetes was not recommended because of insufficient evidence to justify changes to the current list.

Section 21.6: The application requesting deletion of bevacizumab from the EML for ophthalmic indications was rejected. The evidence presented in the application related to risks and harms associated with the compounding and administration of bevacizumab; the importance of sterile compounding and administration of intravitreal bevacizumab was reiterated by the Expert Committee.

Section 22.1: The application requesting deletion of the indication of prevention of postpartum haemorrhage from the listing for misoprostol on the EML was rejected. The application included insufficient new clinical data for the Committee to change the indications for misoprostol on the EML.

Section 26.3: The application requesting addition of ready-to-use therapeutic food to the core list of the EML and EMLc for dietary management of uncomplicated severe acute malnutrition in children was not recommended because of uncertain potential implications of its listing on the EML in terms of availability of alternatives, different manufacturing standards for foods and pharmaceuticals, cost and access.

5. Applications for the 20th Model List of Essential Medicines and the 6th Model List of Essential Medicines for Children

Section 1: Anaesthetics, preoperative medicines and medical gases

1.4: Medical gases (new section)

Oxygen - change: new indication - EML and EMLc

Oxygen **ATC Code: V03AN01**

Proposal

The application proposed an additional indication for oxygen on the EML and EMLc for use as a medical gas for the management of hypoxaemia.

Applicant(s)

PATH

WHO technical department

The WHO departments of Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention, and Infectious Hazard Management supported the inclusion of oxygen on the EML and EMLc for this indication.

EML/EMLc

EML and EMLc

Section

1.4 Medical gases (new section)

Dose form(s) and strength(s)

Inhalation (medical gas)

Core/Complementary

Core

Individual/Square box listing

Individual

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

Oxygen has been included on the EML since 1979 and on the EMLc since 2007. It is currently included in Section 1 Anaesthetics > 1.1 General anaesthetics and oxygen > 1.1.1 Inhalational medicines.

Public health relevance (burden of disease)

Clinical indications for oxygen treatment to reverse or prevent hypoxaemia include surgical anaesthesia, treatment of acute and chronic respiratory conditions, obstetrics, neonatal care, and emergency and critical care (*1*). Surveys in low- and middle-income countries (LMICs) have found that fewer than half of all health facilities have uninterrupted access to oxygen (*2–4*). It has been reported that lack of access to reliable oxygen supplies contributes to preventable deaths, particularly in LMICs. For example, it has been estimated that up to 122 000 deaths from childhood pneumonia could be prevented annually with the strengthening of oxygen supplies (*5*).

Summary of evidence – benefits (from the application)

The application identified numerous existing WHO guidelines in which recommendations are made relating to the use of oxygen (Annex 1 of the application). The rigorous review and decision-making processes of WHO guideline development were acknowledged and a review of GRADE tables from existing WHO guidance documents, insofar as they relate to oxygen use, was conducted. No additional systematic reviews were conducted for the application. WHO recommendations on oxygen use were strong, but based on low- or very low-quality evidence (observational evidence and consensus) in many cases (*6–9*). A meta-analysis of 13 studies involving 13 928 children with acute lower respiratory infection from LMIC found hypoxaemia (defined with oxygen saturation rate (SpO2) below 90%) to be associated with significantly increased risk of death (odds ratio (OR) 5.47; 95% confidence interval (CI) 3.93–7.63). Similarly, an increased risk of death was observed in meta-analysis of three studies involving 673 children with SpO2 less than 92% (OR 3.66; 95% CI 1.42–9.47) (*10*).

Summary of evidence – harms (from the application)

Hyperoxia – excess oxygen supply to, or concentration in, tissues and organs – can result in oxygen toxicity and organ damage. Patients at greatest risk of oxygen toxicity are preterm babies and patients sensitive to hypercapnic respiratory failure (*11*). It is necessary to balance risks of oxygen toxicity against risks associated with targeting lower oxygen saturations, including neurological damage and death, and to optimize therapeutic oxygen delivery to achieve adequate tissue oxygenation. Preterm infants are particularly sensitive to oxygen toxicity and are at increased risk of bronchopulmonary dysplasia, retinopathy of prematurity and subsequent blindness. Careful titration and monitoring of oxygen concentrations is important to prevent these events.

Additional evidence (not in the application)

N/A

WHO guidelines

WHO's 2016 *Oxygen therapy for children: a manual for health workers* (*9*) and 2012 *Recommendations for management of common childhood conditions: newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care* (*8*) make the following key recommendations in relation to oxygen therapy:

- Pulse oximetry is recommended for determining the presence of hypoxaemia and for guiding administration of oxygen therapy to infants and children (strong recommendation, low-quality evidence).
- If oximetry is not available, the following clinical signs could be used to determine use of oxygen therapy: central cyanosis, nasal flaring, inability to drink or feed (when due to respiratory distress), grunting with every breath, depressed mental state (drowsiness, lethargy) (strong recommendation, low-quality evidence)
- In some situations, and depending on the overall clinical condition, children with the following less specific signs may also need oxygen: severe lower chest wall indrawing, respiratory rate greater than 70/min, head nodding (strong recommendation, very low-quality evidence).
- Effective oxygen delivery systems should be a universal standard of care and should be made more widely available (strong recommendation, expert opinion).
- Children with hypoxaemia should receive appropriate oxygen therapy (strong recommendation, low-quality evidence).
- Children with respiratory disease living at ≤2500 m above sea level should receive oxygen therapy if their oxygen saturation is ≤90% as measured by pulse oximetry (strong recommendation, very low-quality evidence).
- In children living at high altitude (>2500 m above sea level), the normal oxygen saturation is lower than in those living at sea level. At high altitude, a lower level of saturation, such as SpO2 ≤ 87%, could be used as a threshold for giving oxygen (recommendation, very low-quality evidence).
- Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, signs of shock, coma or convulsions) should receive oxygen therapy during the resuscitation phase if their SpO2 is <94% (strong recommendation, very low-quality evidence).

WHO's 2012 *Guidelines on basic newborn resuscitation* (*7*) make the following recommendation regarding ventilation of newborns:

- In newly-born term or preterm (>32 weeks' gestation) babies requiring positive-pressure ventilation, ventilation should be initiated with air (strong recommendation, moderate-quality evidence). For preterm babies born at or before 32 weeks' gestation, it is preferable to start ventilation with 30% rather than 100% oxygen. If this is not possible, ventilation should be started with air.

WHO's 2012 *Prevention and control of noncommunicable diseases: guidelines for primary health care in low-resource settings* (*6*) makes the following recommendation regarding use of oxygen in asthma and chronic obstructive pulmonary disease (COPD):

- In the management of exacerbation of asthma, if available, oxygen should be administered to patients with acute severe asthma. This is in keeping with normal practice in high-resource settings where the decision to use oxygen is based on low oxygen saturation readings (strong recommendation, very low-quality evidence).
- In the management of exacerbation of COPD, oxygen, if available, should be administered by a device that controls concentration to 24–28% (strong recommendation, very low-quality evidence).

Costs/Cost–effectiveness

The estimated cost per 1000 L of oxygen from cylinders is reported as US$ 10–30. From oxygen concentrators (devices that concentrate oxygen from ambient air), the estimated cost per 1000 L is US$ 2–8. No estimate of the cost of oxygen from pipeline systems was available.

Total costs for oxygen supply will vary with the options for static or consumable sources, training and maintenance and other associated factors.

Availability

Oxygen is available from cylinders, oxygen concentrators and central pipeline systems.

Other considerations

N/A

Committee recommendations

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.

In addition, the Committee considered that the current title of Section 1, “Anaesthetics”, is not truly representative of the medicines listed in the subsections and therefore recommended that Section 1 be renamed “Anaesthetics, preoperative medicines and medical gases”.

The Expert Committee noted that use of oxygen in the management of hypoxaemia is recommended in numerous WHO and other guidelines, albeit on the strength of low- to very low-quality evidence in many cases. The Committee accepted that there are ethical issues associated with conducting randomized controlled trials (RCTs) of oxygen versus control in acute care settings, and that the lack of RCTs could contribute to the downgrading of the quality of the available evidence. Overall, the Committee considered that it was clinically appropriate to treat hypoxaemic patients with oxygen. The importance of pulse oximetry in the detection and treatment of hypoxaemia was also noted.

The Committee noted the reports of unreliable and limited access to oxygen in many LMICs and considered that inclusion of oxygen on the EML and EMLc for the new indication could, together with other initiatives, contribute to improving the current situation.

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Section 2: Medicines for pain and palliative care

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

Paracetamol – change: new strength – EML and EMLc

Paracetamol **ATC Code: N02BE01**

Proposal
The application requested the addition of a new strength formulation of paracetamol oral liquid (120 mg/5 mL) to the EML and EMLc based on its availability in the market.

Applicant(s)
UNICEF

WHO technical department
N/A

EML/EMLc
EML and EMLc

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

Dose form(s) and strength(s)
Oral liquid: 120 mg/5 mL

Core/Complementary
Core

Individual/Square box listing
Individual

Background (if relevant, e.g. resubmission, previous EC consideration)
Paracetamol oral liquid 125 mg/5 mL has been included on the EML since 1977 and the EMLc since 2007. Other dose forms of paracetamol listed include suppositories and tablets.

Public health relevance (burden of disease)
N/A

Summary of evidence – benefits (from the application)
N/A

Summary of evidence – harms (from the application)

N/A

Additional evidence (not in the application)

N/A

WHO guidelines

N/A

Costs/Cost–effectiveness

The 2014 International Drug Price Indicator Guide reports a median supplier price for paracetamol oral liquid 120 mg/5 mL of US$ 0.0054/mL and a median buyer price of US$ 0.0042/mL. It does not report prices for the 125 mg/5 mL formulation *(1)*.

Availability

UNICEF advised that it procures paracetamol oral liquid as listed on the EML and EMLc (oral liquid 125 mg/5 mL). It stated that most suppliers from it procures paracetamol oral liquid offer the alternative strength of 120 mg/5 mL and proposed the addition of this alternative strength on the basis of market availability.

Paracetamol oral liquid 120 mg/5 mL is widely available globally.

Other considerations

N/A

Committee recommendations

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.

The Committee considered that inclusion of the new strength would assist countries and procurement agencies in their efforts to make appropriate paediatric dose forms of paracetamol available through their national schemes and programmes.

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2.2: Opioid analgesics

Fentanyl – addition – EML; rejection - EMLc

Fentanyl **ATC Code: N02AB03**

Proposal

The application proposed the addition of transdermal fentanyl to the EML and EMLc for treatment of cancer pain.

The proposal formed part of a comparative review of methadone, fentanyl and tramadol for treatment of cancer pain.

Applicant(s)

Dr Carla Ripamonti, Fondazione IRCCS, Instituto Nazionale Tumori, Milan, Italy, and Dr Raffaele Giusti, Medical Oncology Unit, Sant'Andrea Hospital, Rome, Italy

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WHO technical department

WHO Department of Mental Health and Substance Abuse

EML/EMLc

EML and EMLc

Section

2.2 Opioid analgesics

Dose form(s) and strength(s)

The application did not specify the dose forms and strengths proposed for inclusion. The following dose form and strengths are available: transdermal patch 12, 25, 50, 75 and 100 µg/hour.

Core/Complementary

Core

Individual/Square box listing

Individual

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

Fentanyl has not previously been considered for inclusion on the EML/EMLc.

Opioid analgesics included on the EML are codeine and morphine. Only morphine is listed on the EMLc. Hydromorphone and oxycodone are considered alternatives to morphine under a square box listing.

Public health relevance (burden of disease)

Cancer is one of the leading causes of morbidity worldwide, with approximately 14 million new cases in 2012 (*1*). Pain is a frequent and debilitating feature of cancer, occurring across all phases from diagnosis to palliation (*2, 3*). It is estimated that 31.8% of patients with cancer are undertreated for pain (*4*). Opioid therapy is the cornerstone of cancer pain management. The burden of cancer is particularly high in low- and middle-income countries, where 70% of deaths from cancer occur. Patients living in these countries often have limited access to morphine, which is the strong opioid of choice for management of moderate to severe cancer pain.

This application proposed fentanyl as a treatment alternative to morphine to help increase access to opioid pain relief for cancer patients.

Summary of evidence – benefits (from the application)

Fentanyl is a potent synthetic opioid that is suitable for transdermal administration and may provide a useful alternative to morphine for patients with cancer pain. It may be particularly useful for patients unable to take or tolerate oral opioids (e.g. because of malabsorption, dysphagia, vomiting or severe constipation) (*5*) and in patients with renal impairment.

The application presented the findings of a search of the literature published since 2012 on transdermal fentanyl and cancer pain. Only one randomized trial was identified, which compared transdermal fentanyl and pregabalin for neuropathic cancer pain (*6*). A 2013 Cochrane systematic review of nine trials involving 1244 patients assessed the analgesic efficacy and adverse effects of transdermal fentanyl for moderate to severe cancer pain (*7*). The quality of evidence in the included studies was limited, with small numbers and failure to report clinically relevant outcomes. However, the findings of the review led the authors to conclude that, for patients able to tolerate treatment and remain in the study until its end and where data were reported, pain was improved within a short time period and the majority had "no worse than mild pain". Lower rates of constipation were observed with transdermal fentanyl compared with sustained-release morphine (risk ratio (RR) 0.61; 95% CI 0.47–0.78).

A systematic review (*8*) of randomized trials on the effectiveness of opioids for cancer pain in which pain relief was the primary outcome measure concluded that there was fair evidence for the efficacy of transdermal fentanyl, based on a single RCT of fentanyl versus paracetamol plus codeine for management of metastatic bone pain (*9*).

Use of transdermal fentanyl in 64 paediatric (age 2–14 years), opioid-naive cancer patients was analysed in a prospective open-label study (*10*). There was significant improvement in scores on both the visual analogue scale (from 6.82 at baseline to 1.18 by day 15) and FACES pain rating scale (from 6.13 at baseline to 1.13 by day 15). No significant side-effects were reported and the authors concluded that transdermal fentanyl was an effective, safe and well-tolerated treatment for paediatric cancer patients.

Summary of evidence – harms (from the application)

Common adverse effects associated with opioid therapy are also seen with fentanyl,

including respiratory effects, nausea, vomiting, constipation and somnolence. Rash, application site reactions and itch have also been reported with the transdermal formulation (*5*). Transdermal fentanyl may cause less constipation than oral morphine (*7*).

Severe diarrhoea associated with transdermal fentanyl during the first 72 hours of treatment has been reported (*11*).

Additional evidence (not in the application)

Transdermal fentanyl and sustained-release oral morphine were compared in opioid-naive patients with moderate to severe cancer pain and in opioid-experienced patients with mild to moderate pain (*12*). The two drugs showed equal efficacy in terms of pain control and improved sleep quality. Fentanyl was better tolerated than morphine, with fewer fentanyl-treated patients reporting constipation or discontinuing the trial. Patient and investigator global evaluation of treatment also favoured fentanyl for "troublesome side-effects" and "less interruption of daily activities". The authors concluded that transdermal fentanyl is as effective as, but better tolerated than, sustained-release morphine as first-choice opioid for treatment of cancer pain.

Another study compared fentanyl, morphine and methadone in the management of cancer pain (*13*). All three drugs were found to be similarly effective and well tolerated. There were no differences in pain intensity between the three treatment groups, or in consumption of non-opioid analgesics, at any time point. No relevant differences in quality-of-life scores, symptom intensity or distress scores were observed between treatment groups.

Residual fentanyl in used transdermal patches after 72 hours has been reported to be between 28% and 84.4% (*14, 15*). Potential for harms, misuse and abuse is associated with residual fentanyl in used patches and appropriate, safe disposal is essential.

WHO guidelines

The WHO guidelines for management of cancer pain are currently under review.

WHO's 2012 guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (*16*) recommend the use of strong opioid analgesics for the relief of moderate to severe persisting pain in children (strong recommendation, low-quality evidence). Morphine is recommended as the first-line treatment choice. There is insufficient evidence to support recommendation of alternative opioids as first choice. The guidelines go on to recommend switching opioids and/or route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, low-quality evidence). Alternative opioids listed in the guidelines are fentanyl, hydromorphone, methadone and oxycodone. Oral administration is recommended.

Costs/Cost–effectiveness

No information regarding costs or cost–effectiveness was provided in the application.

In a cross-sectional study of the global availability and prices of five opioids (morphine, methadone, fentanyl, hydromorphone and oxycodone), oral methadone was found to be the least expensive, with a median price of US$ 0.5 for 30 days of treatment (*17*). The

median price of transdermal fentanyl for 30 days of treatment was US$ 2.2 while that of immediate-release oral morphine tablets/capsules was US$ 18.9.

Availability

Fentanyl, like morphine, is subject to international control under the Single Convention on Narcotic Drugs, 1961.

Other considerations

WHO is currently developing new cancer pain guidelines, which are due for completion in late 2017 or early 2018.

Committee recommendations

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.

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Methadone - change: new indication - EML; addition - EMLc

Methadone **ATC Code: N07BC02**

Proposal

The application proposed the addition of methadone to the EML and EMLc for treatment of cancer pain.

The proposal formed part of a comparative review of methadone, fentanyl and tramadol for treatment of cancer pain.

Applicant(s)

Dr Carla Ripamonti, Fondazione IRCCS, Instituto Nazionale Tumori, Milan, Italy, and Dr Raffaele Giusti, Medical Oncology Unit, Sant' Andrea Hospital of Rome, Italy

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WHO technical department

WHO Department of Mental Health and Substance Abuse

EML/EMLc

EML and EMLc

Section 2.2 Opioid analgesics Dose form(s) and strength(s)

The application does not specify the dose forms and strengths proposed for inclusion. The following oral dose forms and strengths are available:

- tablet: 5 mg, 10 mg (as hydrochloride)
- oral liquid: 1 mg/mL, 2 mg/mL (as hydrochloride)
- oral concentrate: 5 mg/mL, 10 mg/mL (as hydrochloride)

Core/Complementary

Core

Individual/Square box listing

Individual

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

Methadone oral liquid is currently included in the EML for use in opioid dependence.

Opioid analgesics included on the EML are codeine and morphine. Only morphine is listed on the EMLc. Hydromorphone and oxycodone are considered as alternatives to morphine under a square box listing.

Public health relevance (burden of disease)

Cancer is one of the leading causes of morbidity worldwide, with approximately 14 million new cases in 2012 (*1*). Pain is a frequent and debilitating feature of cancer, occurring across

all phases from diagnosis to palliation (*2, 3*). It is estimated that 31.8% of patients with cancer are undertreated for pain (*4*). Opioid therapy is the cornerstone of cancer pain management. The burden of cancer is particularly high in low- and middle-income countries, where 70% of deaths from cancer occur. Patients living in these countries often have limited access to morphine, the strong opioid of choice for management of moderate to severe cancer pain.

This application proposed methadone as a treatment alternative to morphine to help increase access to opioid pain relief for cancer patients.

Summary of evidence – benefits (from the application)

Analgesic treatment guidelines often consider morphine and other opioids to be comparable and interchangeable in the treatment of chronic cancer pain, although individual responses to these medicines may vary. A study comparing the analgesic efficacy of oral morphine, oral oxycodone, transdermal fentanyl and transdermal buprenorphine found similar levels of pain relief with the four medicines but varying proportions of patients classified as non-responders or poor responders. In addition, all patients required continuous dose adjustments to achieve good analgesic response, and patients treated with morphine often required switching to alternative opioids. Adverse effects were similar except for CNS effects, which were more common with morphine (*5*).

Compared with morphine, methadone has similar affinity for mu- and kappa-opioid receptors and greater affinity for delta-opioid receptors (*6, 7*). Unlike morphine, methadone also blocks NMDA (*N*-methyl-D-aspartate) receptors and inhibits neuronal serotonin and norepinephrine reuptake, thereby inhibiting nociceptive transmission (*8, 9*). The analgesic effect of methadone is probably mediated by synergistic mechanisms that are different from those of morphine.

The pharmacokinetics of methadone differ significantly from those of morphine. Methadone has higher oral bioavailability and protein binding and a longer elimination half-life. It is metabolized primarily in the liver to inactive metabolites whereas morphine is metabolized primarily in the kidney and has active metabolites. Methadone may represent an alternative treatment option to morphine in patients with renal disease.

The application presented the findings of a search of the literature published since 2012 on methadone and cancer pain. Randomized controlled trials (RCTs) demonstrated the analgesic benefits of methadone in cancer pain patients who were intolerant to, or had inadequate pain relief from, other strong opioids (*10*) and in patients with head and neck cancer who were experiencing neuropathic pain and were naive to strong opioids (*11*). In addition, a series of systematic reviews, published between 2012 and 2016, were identified that investigated methadone for cancer in various circumstances including patients receiving methadone maintenance therapy for opioid addiction, rotation from other opioids, and elderly patients. Most of these systematic reviews determined the level of evidence to be low. In a 2014 systematic review of RCTs of methadone in cancer pain, the authors stated that differences in methodology and study design made it impossible to draw definite conclusions regarding the efficacy or safety of, or rotation strategies for, methadone (*12*).

The application also briefly presents findings from a series of retrospective studies,

prospective, open-label studies, observational studies and case reports/series. Heterogeneity in outcome measures, methodology and evaluation tools was noted. A retrospective study on the safety and efficacy of methadone in a palliative care unit in Argentina found methadone to be a preferable first-line treatment for cancer-related pain because of its effectiveness at low cost (*13*). Compared with other opioids, methadone was associated with less opioid rotation (15% versus 50%) and with a longer time to opioid rotation (20.6 versus 9.0 days). In a prospective, open-label study, efficacy and safety of methadone as second-line opioid therapy were assessed in adults with cancer at a palliative care outpatient clinic (*14*). After rotation to methadone, pain scores decreased significantly and no increase in opioid toxicity was observed.

Summary of evidence – harms (from the application)

The pharmacokinetics of methadone are very different from those of morphine and are less predictable, varying widely among individuals. Accumulation occurs with repeated dosing and so adverse effects are delayed over time (*15–17*). The terminal elimination half-life of methadone varies from 13 to 58 hours (and up to 120 hours in some patients) compared with 3–4 hours for morphine (*18*). This long half-life makes dose adjustment more difficult with methadone than with morphine, necessitating specialist supervision to establish the optimum dosing regimen. No evidence on pharmacokinetics in children was provided in the application.

Methadone is also more likely than morphine to give rise to drug–drug interactions with common cancer treatments because it is metabolized by the cytochrome P-450 enzyme group.

Methadone is associated with cardiac toxicities through its effects on cardiac conduction – QTc prolongation, torsades de pointes, ventricular fibrillation (*19, 20*). However, at clinically effective analgesic doses, methadone dosage and duration were found not to be correlated with QTc prolongation, even in the presence of other risk factors *(20)*.

Additional evidence (not in the application)

In 1986, methadone was compared with morphine in a 14-day randomized open-label study (*21*). Analgesic effects were similar, as was the pattern of adverse effects; methadone dose was relatively stable (4–24 mg/day) while a substantial increase in dose was reported in patients given morphine. Similar results were achieved in a subsequent study in the same year (*22*) and again in a prospective randomized study that compared the analgesic and adverse effects and the doses of methadone with those of morphine (*23*).

A randomized, double-blind controlled trial compared the effectiveness and safety of methadone and morphine as first-line opioids for cancer pain (*24*). One hundred and three patients were randomly assigned 1:1 to morphine or methadone. The groups had similar baseline scores for pain, sedation, nausea, confusion and constipation. There was a 56% responder rate in the morphine group for a pain response of 20% and 49% for the methadone group. Methadone did not show superior analgesic efficiency or overall tolerability at 4 weeks compared with morphine as a first-line strong opioid for the treatment of cancer pain, and the authors concluded that methadone had comparable

efficacy to morphine with more adverse effects and a higher number of dropouts (40.8% vs 31.5%).

These studies, and another randomized trial in 2008 (*25*), showed methadone to have an analgesic effect comparable, but not superior, to that of morphine, with a similar adverse effect profile. Over time, the opioid escalation index was lower for methadone than for morphine, which may explain the reduced tolerance of methadone with respect to morphine.

A 2014 systematic review focused on the role of methadone in pain management in elderly patients (*26*). Seven articles were identified but none was specific to methadone use in elderly patients with cancer. There are insufficient data on the use of methadone as an analgesic in elderly people with cancer.

Two methadone titration methods (stop-and-go and progressive) were compared in patients with cancer-related pain who were intolerant to, or whose pain was inadequately relieved by, Level 3 opioids (*10*). The primary end-point was the rate of success or failure at Day 4, defined as pain relief and no overdose. Pain relief was obtained in 80% of patients and the rate of success/failure was approximately 40% at Day 4 in both groups. The authors concluded that methadone is an effective and sustainable second-line alternative opioid for the treatment of cancer-related pain and that the two methods of titration are comparable in terms of efficacy and safety.

Methadone and fentanyl were compared in a randomized trial of 52 strong-opioid-naive patients with head and neck cancer, pain >4 on the Numerical Rating Scale (NRS) and a neuropathic pain component (*11*). The primary outcomes were reduction in average pain, clinical success (defined as 50% average pain decrease) and reduction in pain interference. Reduction in NRS was higher with methadone than with fentanyl at 1, 3 and 5 weeks; the difference was significant at weeks 1 and 3 and represented the first evidence of efficacy of methadone versus fentanyl in cancer patients with a neuropathic pain component

A 2017 Cochrane systematic review of the effectiveness and tolerability of methadone in cancer pain, published after closure of the EML application period, included six studies with 388 participants (*27*). This review was an update of one done in 2006. It did not include any studies in children. Heterogeneity in methods and comparisons meant that pooled quantitative synthesis of results was not possible. For the main comparison of methadone with morphine, one study of 103 participants reported better than 20% improvement in pain scores for 75% and 76% of participants, respectively. In another study of 54 participants, all patients reported achieving “no worse than mild pain” (i.e. pain score of 3 or less after treatment) based on mean pain scores. Two studies of 148 participants reported mean scores close to 3. The quality of the evidence was considered to be low, downgraded because of risk of bias (random allocation and allocation concealment unclear, small sample sizes) and imprecision (small sample sizes, wide confidence intervals around estimates of effect). The risk of adverse events (relating to appetite, thirst, somnolence) could not be estimated and the quality of evidence was rated very low, downgraded because of the risk of bias and imprecision (as for efficacy) and also for indirectness, with surrogate measures being used for the outcomes of interest.

The authors concluded that, based on low-quality evidence, methadone has similar

analgesic benefits to morphine and has a role in the management of cancer pain in adults. They further concluded that morphine and fentanyl may be easier opioids to manage but may be more expensive than methadone in many countries.

WHO guidelines

The WHO guidelines for management of cancer pain are currently under review.

WHO's 2012 guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (*28*) recommend the use of strong opioid analgesics for the relief of moderate to severe persisting pain in children (strong recommendation, low-quality evidence). Morphine is recommended as the first-line treatment choice. There is insufficient evidence to support a recommendation of alternative opioids as first choice. The guidelines also recommend switching opioids and/or route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, low-quality evidence). Alternative opioids listed in the guidelines are fentanyl, hydromorphone, methadone and oxycodone. Oral administration is recommended.

Costs/Cost–effectiveness

No information regarding costs or cost–effectiveness was provided in the application.

The MSH (Management Sciences for Health) *International Medical Products Price Guide* reports a median unit price for methadone oral solution 5 mg/mL of US$ 0.0210/mL. The median unit price for morphine sulfate 10-mg tablet or capsule is reported as US$ 0.1247 (*29*).

In a cross-sectional study of the global availability and prices of opioids (*30*), oral methadone was found to be the least expensive of the five opioids studied (morphine, methadone, fentanyl, hydromorphone and oxycodone), with a median price of US$ 0.5 for 30 days of treatment. In comparison, the median price for 30 days treatment with immediate-release oral morphine tablets/capsules was US$ 18.9.

Availability

Methadone, like morphine, is subject to international control under the Single Convention on Narcotic Drugs, 1961.

Other considerations

WHO is currently developing new cancer pain guidelines, which are due for completion late 2017 or early 2018.

Committee recommendations

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.

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Tramadol – rejection – EML and EMLc

Tramadol — ATC Code: N02AX02

Proposal

The application proposed the addition of tramadol to the EML and EMLc for treatment of cancer pain.

The proposal formed part of a comparative review of methadone, fentanyl and tramadol for the treatment of cancer pain.

Applicant(s)

Dr Carla Ripamonti, Fondazione IRCCS, Instituto Nazionale Tumori, Milan, Italy, and Dr Raffaele Giusti, Medical Oncology Unit, Sant' Andrea Hospital of Rome, Italy

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WHO technical department

WHO Department of Mental Health and Substance Abuse

EML/EMLc

EML and EMLc

Section

2.2 Opioid analgesics

Dose form(s) and strength(s)

The application did not specify the dose forms and strengths proposed for inclusion. The following dose forms and strengths are available:

- capsule (immediate release): 50 mg (as hydrochloride)
- oral liquid: 100 mg/mL (as hydrochloride)
- injection: 50 mg/mL in 2-mL ampoule (as hydrochloride)
- tablet or capsule (controlled release): 50 mg; 100 mg; 150 mg; 200 mg; 300 mg; 400 mg (as hydrochloride)

Core/Complementary

Core

Individual/Square box listing

Individual

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

Tramadol had not previously been considered for inclusion on the EML/EMLc.

Opioid analgesics included on the EML are codeine and morphine. Only morphine is listed on the EMLc. Hydromorphone and oxycodone are considered as alternatives to morphine under a square box listing.

Tramadol is a synthetic opioid agonist with affinity for mu-opioid receptors. It also has non-opioid properties, through inhibition of serotonin and norepinephrine reuptake, which are thought to contribute to its analgesic effect (*1*). It is less potent than morphine: relative potency of morphine to tramadol is reported as around 4:1 or 5:1 with oral dosing and 10:1 with parenteral dosing (*2, 3*).

Public health relevance (burden of disease)

Cancer is one of the leading causes of morbidity worldwide, with approximately 14 million new cases in 2012 (*4*). Pain is a frequent and debilitating feature of cancer, occurring across all phases from diagnosis to palliation (*5, 6*). It is estimated that 31.8% of patients with cancer are undertreated for pain (7). Opioid therapy is the cornerstone of cancer pain management. The burden of cancer is particularly high in low- and middle-income countries (LMICs), where 70% of deaths from cancer occur. Patients living in these countries often have limited access to morphine, the strong opioid of choice for management of moderate to severe cancer pain.

This application proposed tramadol as a treatment alternative to morphine to help increase access to opioid pain relief for cancer patients. It noted that, while the available evidence on the use of tramadol in cancer pain is poor, oral tramadol is often available in countries where morphine is not (because of international control, regulatory scheduling, licensing and other restrictions).

Access to adequate opioids to deliver appropriate pain management is poor or non-existent in many countries, particularly LMICs (*8, 9*).

Summary of evidence – benefits (from the application)

The application presented the findings of a search of the literature published in the past five years on tramadol and cancer pain.

One study randomized 240 opioid-naive patients with cancer to receive either a weak opioid (tramadol, tramadol in combination with paracetamol, or a fixed-dose combination of paracetamol and codeine) or low-dose oral morphine for 28 days (*10*). The primary end-point was the number of "responders" at 28 days or the end of observation, whichever came first. Responders were defined as patients who experienced a 20% or greater reduction in pain intensity from baseline. The primary end-point was achieved in 88.2% of the morphine group and 54.7% of the weak opioid groups (odds ratio (OR) 6.18; 95% confidence interval (should read (CI) 3.12 –12.24; $P < 0.001$).

A systematic review of randomized trials on the effectiveness of opioids for cancer pain, in which pain relief was the primary outcome measure, found that there was poor evidence for the efficacy of tramadol (*11*). The conclusion was based on three low-quality studies.

In a prospective open-label study, the efficacy of a fixed-dose combination of tramadol and paracetamol was evaluated in 353 advanced cancer patients (*12*). The combination was found to be effective in the treatment of chronic cancer pain, with acceptable tolerability.

Average pain scores were significantly lower from 24 hours after the start of treatment.

The evidence presented in the application for tramadol was highly heterogeneous: the different comparisons, outcome measures and effect scales used made it difficult to accurately determine the magnitude of benefit.

Summary of evidence – harms (from the application)

The adverse effects commonly associated with opioid therapy are also seen with tramadol, including sedation, constipation and respiratory depression.

Severe respiratory depression associated with tramadol has been reported in children (*13*) and in one case report of an adult with cancer pain and renal insufficiency (*14*). Hyponatraemia has also been observed during tramadol treatment (*15–17*). At normal doses, tramadol has been associated with seizures (*18*).

Serotonin toxicity may occur when tramadol is given concomitantly with, or within 14 days of, monoamine oxidase inhibitors and other medicines that increase serotonin activity (*19*).

Tramadol abuse and trafficking have become a serious problem in many countries where the drug is widely available and not subject to stricter controls, particularly in Africa and the Middle East and in parts of Asia, as noted in the 2015 report of the United Nations International Narcotics Control Board (*20*).

Additional evidence (not in the application)

In a randomized controlled trial (RCT) that compared morphine with weak opioids for moderate cancer pain, both treatments were found to be well tolerated (*10*). No differences were observed in the intensity and frequency of opioid-related effects between treatment groups, and there were few discontinuations due to adverse events.

In another RCT, tramadol 200 mg/day was compared with hydrocodone + acetaminophen 25 mg + 2500 mg/day in 118 patients with chronic cancer pain (*21*). There was no statistically significant difference between the two treatment arms in terms of analgesic efficacy. However, the incidence of side-effects such as nausea (relative risk (RR) 1.69; 95% CI 1.03–2.77), vomiting (RR 2.21; 95% CI 1.14–4.32) and dizziness (RR 2.12; 95% CI 1.17–3.86) was significantly higher in the tramadol arm. Similar results were found in another RCT which compared the incidence of adverse events associated with oral tramadol, hydrocodone and codeine in 177 patients with cancer pain (*22*).

The abuse potential of tramadol, both in experienced drug users and in patients with no history of substance abuse, has been raised in recent studies (*23, 24*).

WHO guidelines

The WHO guidelines for management of cancer pain are currently under review.

WHO's 2012 guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (*25*) recommend the use of strong opioid analgesics for the relief of moderate to severe persisting pain in children (strong recommendation, low-quality evidence). Morphine is recommended as the first-line treatment choice. There is insufficient

evidence to support a recommendation of alternative opioids as first choice. The guidelines also recommend switching opioids and/or route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, low-quality evidence). Alternative opioids listed in the guidelines are fentanyl, hydromorphone, methadone and oxycodone. Oral administration is recommended.

Costs/Cost–effectiveness

No information regarding costs or cost–effectiveness was provided in the application.

The MSH (Management Sciences for Health) *International Medical Products Price Guide* reports a median unit price for tramadol hydrochloride 50-mg tablet/capsule of US$ 0.0427. The median unit price for morphine sulfate 10-mg tablet or capsule is reported as US$ 0.1247 (*26*).

Availability

Unlike morphine, tramadol is not subject to international control under the Single Convention on Narcotic Drugs, 1961. Preliminary results (unpublished) of a price and availability survey conducted by WHO in the Democratic Republic of the Congo indicated that controlled-release oral morphine was available in only 1 of 85 facilities sampled, while immediate-release morphine was not available in any of them. In comparison, immediate- and controlled-release tramadol was available in 26 and 11 of the 85 facilities sampled, respectively.

Other considerations

WHO is currently developing new cancer pain guidelines which are due for completion in late 2017 or early 2018.

Committee recommendations

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.

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2.3: Medicines for other common symptoms in palliative care

Gabapentin – rejection – EML

Gabapentin **ATC Code: N03AX12**

Proposal

The application proposed the addition of gabapentin to the core list of the EML as an analgesic agent for the management of neuropathic pain (central and peripheral) in adults.

Applicant(s)

Peter R Kamerman, Nanna Finnerup, Liliana De Lima, Simon Haroutounian, Srinivasa Raja, Andrew Rice, Blair Smith, Rolf-Detlef Treede

International Association for the Study of Pain (IASP)

International Association of Hospice and Palliative Care (IAHPC)

WHO technical department

Department of Mental Health and Substance Abuse

EML/EMLc

EML

Section

2.3 Medicines for other common symptoms in palliative care

Dose form(s) and strength(s)

Oral dose forms, tablets and capsules: 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

In 2017 the Expert Committee examined four medicines for pain and palliative care for the first time: methadone, fentanyl, tramadol and gabapentin.

Public health relevance (burden of disease)

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system" (*1, 2*). It is commonly associated with back pain (e.g. lumbar or cervical radiculopathy), diabetes (painful diabetic neuropathy), post-surgical pain, HIV-AIDS, and herpes zoster (post-herpetic neuralgia) but can also arise through many other diseases or injuries. Specific clinical features include symptoms such as paraesthesia, burning or shooting pains, altered sensation (numbness, allodynia or hyperalgesia) and locally altered autonomic function (*3*).

In the absence of both a "gold standard" for defining cases and a clinical code for routine health-care use, it is impossible to identify the precise prevalence of neuropathic pain, for example through the 2013 Global Burden of Disease study (*4*). The application provided estimates of prevalence based on specific causes of neuropathic pain (e.g. diabetes) or on self-reports of some symptoms, assuming prevalence in the overall population of the order of 7–10% (*5*). The estimates provided appear to substantially overestimate the burden of disease. Few studies evaluated the incidence through appropriate methods, particularly use of a standard process to confirm diagnosed cases in general populations. In two European studies (*6, 7*), the incidence per 10 000 person-years was 3.0 (95% confidence interval (CI) 3.0–3.1) and 4.2 (95% CI 3.8–4.5) for post-herpetic neuralgia, 2.8 (95% CI 2.7–2.8) and 7.2 (95% CI 6.7–7.7) for painful diabetic neuropathy, and 0.11 (95% CI 0.09–0.12) and 0.22 (95% CI 0.15–0.33) for phantom limb pain. These estimates differ considerably from those provided in the application and seem to be more reliable. The incidence of these three conditions increased with age.

Neuropathic pain has a significant adverse impact on all measured aspects of life, health and function (*8*), irrespective of the underlying diagnosis (*9*).

Summary of evidence – benefits (from the application)

The application included data on the following medicines: tricyclic antidepressants (TCAs; amitriptyline), serotonin–norepinephrine re-uptake inhibitors (SNRIs; mainly duloxetine), pregabalin and gabapentin. All were considered to be first-line options for neuropathic pain, but amitriptyline is the only one currently included in the EML.

The evidence supporting the application was based on a recent systematic review, meta-analysis and GRADE-based recommendations (*10*). The review searched for full reports of randomized, controlled, double-blind studies published in peer-reviewed journals between 1966 and 2014 and for unpublished trials. A supplementary search of PubMed was conducted on 26 February 2016 to update the application results.

The population included in the trials comprised patients of any age with neuropathic pain according to the IASP definition (i.e. pain caused by a lesion or disease of the somatosensory nervous system) (*2*).

The interventions considered were systemic or topical treatments (oral, sublingual, oropharyngeal, intranasal, topical, subcutaneous, intradermal, and smoking) lasting at least 3 weeks. Single-administration treatments with long-term efficacy (high-concentration capsaicin 8% patches, botulinum toxin) were included if there was a minimum follow-up of 3 weeks. Studies in which intramuscular, intravenous or neuraxial

routes of administration were used and those of pre-emptive analgesia were excluded. Randomized, double-blind, placebo-controlled studies with parallel group or crossover study designs were included; studies in which the primary outcome measure was not pain were excluded.

Quality was assessed using the five-point Oxford Quality Scale (*11*). Additional dimensions assessed for risk of bias were: allocation concealment, incomplete accounting of outcome events, selective outcome reporting, stopping early for benefit, use of invalidated outcome measures, carry-over effects in crossover trials, and inadequate sample size.

A total of 229 reports, across a number of agents, were included in the published meta-analysis (*10*); 127 (55%) of the 229 trials were in patients with diabetic painful polyneuropathy or post-herpetic neuralgia. The mean Oxford Quality Scale score was 4.1 (SD 0.87; range 2–5). Studies were associated with potential or established major shortcomings in several areas – incomplete outcome data, size, duration and outcome reported.

The application identified publication bias through funnel plots and Egger regression as a potential distortion of the results. It used the "trim and fill" method to correct for funnel plot asymmetry arising from publication bias; this method suggested 34 theoretically missing studies. The overall effect size of benefit was reduced from an odds ratio (OR) of 1.8 (95% CI 1.7–1.9) to OR 1.6 (95% CI 1.5–1.7). This suggests about a 25% overstatement of treatment effects on pain reduction. The correction was applied to all studies, irrespective of individual medicines. It is possible that the correction of benefit associated with studies evaluating gabapentin is different from that of studies evaluating the other pharmacotherapies. Furthermore, susceptibility-to-bias analyses, another approach used to deal with publication bias, assume that results in published studies are unbiased, which is not the case.

With regard to risk of bias and publication bias, the application overlooked data (see "Additional evidence" section below), while heterogeneity was not presented.

The number needed to treat (NNT) to achieve 50% pain relief non-attributable to placebo for the evaluated medications ranged between 4 and 9: amitriptyline 4.3 (95% CI 3.6–5.3), gabapentin 6.3 (95% CI 5.0–8.3), pregabalin 8.8 (95% CI 7.5–10.8), SNRIs 6.4 (95% CI 5.2–8.4).

In total, the assessment was based on 14 randomized controlled trials of gabapentin (900–3600 mg/day). The trials were conducted predominantly in patients with post-herpetic neuralgia, painful polyneuropathy (mainly diabetic), spinal cord injury, post-amputation pain and peripheral nerve injury.

The combined NNT for gabapentin across the 14 studies was 6.3 (95% CI 5.0–8.3), and there was no evidence of a dose–response effect.

The application also provided data on head-to-head trials of gabapentin and TCAs, showing conflicting results. One trial reported that gabapentin had lower efficacy than amitriptyline in the management of neuropathic pain resulting from spinal cord injury (*12*), while two others reported no difference in treatment efficacy between gabapentin and nortriptyline or amitriptyline (*13, 14*).

The application also mentioned a Cochrane systematic review (*15*) that partitioned the

analysis according to pain etiology and considered the overall evidence for benefits and harms at some risk of bias. Data were largely concordant: gabapentin was considered effective in post-herpetic neuralgia (NNT 8.0; 95% CI 6.0–12) and painful diabetic neuropathy (NNT 5.9; 95% CI 4.6–8.3). The authors concluded that there were insufficient data in other pain conditions, including fibromyalgia, to allow any reliable conclusion to be reached.

Summary of evidence – harms (from the application)

Analysis of adverse effects in trials of gabapentin for neuropathic pain was based on a meta-analysis of 11 studies (*10*); the combined number needed to harm (NNH) was 25.6 (95% CI 15.3–78.6). The NNH was calculated as the number of patients who needed to be treated for one patient to drop out because of adverse effects. When specific adverse events were examined, dizziness, somnolence (or drowsiness or sedation) and, in a few studies, peripheral oedema and confusion had a prevalence of >10%, higher than in the placebo group. The NNH for dizziness was 5.1 (95% CI 4.3–6.3) and for somnolence 7.1 (95% CI 5.7–9.4).

In the Cochrane review of gabapentin in fibromyalgia and neuropathic pain (*15*), 62% of gabapentin-treated patients and 50% of those given placebo experienced at least one adverse event in 17 studies with 4002 participants. The risk ratio (RR) for adverse events was 1.25 (95% CI 1.2–1.3) and the NNH was 8.6 (95% CI 6.8–12). Serious adverse events were no more common for gabapentin than for placebo (RR 1.2; 95% CI 0.8–1.7). The NNH for somnolence, drowsiness or sedation was 11 (95% CI 9.4–14; 4125 participants), for dizziness 7.6 (95% CI 6.6–8.8; 4125 participants) and for peripheral oedema 21 (95% CI 16–30; 3220 participants). Gabapentin was associated with an increased risk of ataxia or gait disturbance with an NNH of 13 (95% CI 9–24; 544 participants) (*15*).

Additional evidence (not in the application)

In 1993, gabapentin (Neurontin®, Pfizer) was first approved by the U.S. Food & Drug Administration (FDA) as an adjunctive therapy for epilepsy. In 2002, the drug was approved for the management of post-herpetic neuralgia, its only pain-related indication.

Parke-Davis and Pfizer, the companies responsible for promoting and marketing gabapentin, adopted a publication strategy "to disseminate the information as widely as possible through the world's medical literature" (*16*). This promotion was judged to be illegal and fraudulent: in 2004, American pharmaceutical manufacturer Warner-Lambert pleaded guilty and agreed to pay more than US$ 430 million to resolve criminal charges and civil liabilities in connection with its Parke-Davis division's marketing scheme of unapproved uses of gabapentin (*17*). This was one of the largest settlements reached between the United States Department of Justice and pharmaceutical companies.

Following litigation, internal company documents relating to gabapentin publication strategy have been made publicly available through two separate legal actions (*18, 19*). These sources were analysed in a series of studies (*20–23*) that documented publication and outcome reporting biases and data manipulation. The magnitude of these biases is highly relevant, and affects the evidence presented in the application.

Firstly, in 2009, of 20 clinical trials for which internal documents were available from Pfizer and Parke-Davis, eight were never published.

Secondly, there were irreconcilable differences between the original protocols, statistical analysis plans, interim research reports and the main publications relating to most trials. For eight of the 12 published trials, the primary outcome defined in the published report differed from that described in the protocol. In three out of 10 trials, the numbers of participants randomized and analysed for the primary outcome and the type of analysis for efficacy and safety in the internal research report and the trial publication differed. Different subsets of participants were included in the analysis, leading to different findings: in one trial, the main findings in the publication did not include data from 40% of participants actually randomized. These changes are likely to have unbalanced the comparisons, favouring responsive patients and excluding poor responders in the arms allocated to gabapentin, thereby inflating the size of the effect attributable to the drug.

The important differences between the internal and published documents about the number of patients or the plans of the analyses invalidate the study design (i.e. downgrading the evidence from experimental to observational), as the randomization is no longer valid.

WHO guidelines

Currently there are no WHO guidelines for the treatment of neuropathic pain.

Guidelines from the IASP Special Interest Group on Neuropathic Pain (NeuPSIG) (10), the United Kingdom National Institute for Health and Care Excellence (NICE) (24) and the European Federation of Neurological Societies (25) report that TCAs, α2δ calcium channel ligands (gabapentin and pregabalin), and selective SNRIs should be considered as first-line therapy, with the choice of medicine being guided by clinical and therapeutic factors (e.g. contraindications, interactions), and by medicine availability and affordability.

Costs/Cost–effectiveness

Comparative pricing data were obtained from the MSH (Management Sciences for Health) *International Medical Products Price Guide* (*26*). Prices based on the defined daily dose (DDD) of gabapentin varied from US$ 0.36 to US$ 2.31; prices of amitriptyline varied from US$ 0.04 to US$ 0.34.

Analysis of comparative pricing for gabapentin was limited by the absence of price data from suppliers, and price data were available from only one buyer source each for the 100-mg and 400-mg doses of gabapentin and three for the 300-mg dose.

Cost–utility analysis

NICE recently completed a cost–utility analysis across treatments typically recommended as first-line for neuropathic pain (*24*). Medicine prices were taken from the March 2013 Electronic Drug Tariff register of the United Kingdom National Health Service, and health benefit was valued in quality-adjusted life-years (QALYs). All medicines were associated with positive incremental net monetary benefits, assuming a QALY value of £20 000 and £30 000. Based on the outcome of the cost–utility analysis, the NICE Guideline Development

Group recommended gabapentin and amitriptyline as initial treatment options for neuropathic pain.

Availability

Gabapentin has regulatory approval as a prescription-only medicine from: FDA, European Medicines Agency (EMA), Australian Therapeutic Goods Administration (TGA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada. However, FDA indication is limited to post-herpetic neuralgia, and PMDA and Health Canada indicate gabapentin only for the treatment of epilepsy.

Regulatory approval of gabapentin for neuropathic pain

Regulatory authority	*Indication for pain*
FDA, USA	Post-herpetic neuralgia
EMA, European Union	Neuropathic pain
TGA, Australia	Neuropathic pain
PMDA, Japan	No
Health Canada	No

Other considerations

The Committee acknowledged the importance of the issues of publication and outcome reporting bias.

Committee recommendations

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.

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Section 5: **Anticonvulsants/antiepileptics**

Lamotrigine – addition – EML and EMLc

Lamotrigine — ATC Code: N03AX09

Proposal

The application proposed the addition of lamotrigine to the core list of the EML and EMLc as:

- second-line therapy for the treatment of partial or generalized epilepsy refractory to monotherapy with one of the antiepileptic medicines already included in the EML/EMLc;
- monotherapy for women of childbearing age with new-onset generalized epilepsy when the severity of the disease makes therapy with antiepileptic medicines strongly recommended;
- monotherapy for persons with HIV/AIDS taking antiretroviral agents presenting with new-onset partial or generalized epilepsy.

Applicant(s)

Francesco Nonino, Giulio Formoso, Roberta Giroldini, Lucia Magnano, Elisabetta Pasi, Anna Maria Marata, Medicines and Medical Devices Area, Health Care and Welfare Directorate Community Care Service, Emilia Romagna Health and Social Agency, Bologna, Italy – WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development

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WHO technical department

Department of Mental Health and Substance Abuse

EML/EMLc

EML and EMLc

Section

5. Anticonvulsants/antiepileptics

Dose form(s) and strength(s)

Tablet: 25 mg, 50 mg, 100 mg, 200 mg

Tablet (chewable, dispersible): 2 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg

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Core/Complementary

Core

Individual/Square box listing

Individual

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

The EML currently lists nine anticonvulsant medicines: carbamazepine, diazepam, lorazepam, magnesium sulfate, midazolam, phenobarbital, phenytoin, valproic acid and ethosuximide (the last is on the Complementary List only). Apart from magnesium sulfate, the same medicines are on the EMLc. These medicines are intended to treat generalized and partial epilepsy, mostly as first-line therapies.

In the past, the Expert Committee has recommended a review of second-line anticonvulsants for an update of the EML, including topiramate, lamotrigine and gabapentin as second-line therapy for children and adults (*1*).

None of the anticonvulsants that are not included in the EML and EMLc can be considered as the treatment of choice in both generalized and partial seizures; "treatment strategy should be individualized according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the child, young person or adult's lifestyle, and the preferences of the person and their family and/or carers as appropriate" (*2*). Inclusion in the EML/EMLc of suitable treatments that may be added as second-line therapies in drug-resistant epilepsy, and also used as alternative first-line options if treatments now included in the EML/EMLc are unavailable or not tolerated, is desirable.

The application was preceded by an overview of recently updated guidance on epilepsy, which found that lamotrigine is generally mentioned among first-choice treatment options in generalized and focal seizures, both as monotherapy in newly diagnosed epilepsy and as an adjunctive treatment in refractory disease. Lamotrigine was therefore selected as a priority candidate for the EML, given its broad indications in children and adults, its safety profile in pregnant women, and the fact that it is generally recommended by evidence-based clinical guidelines.

Lamotrigine (LTG) (3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine) is a phenyltriazine antiepileptic drug and chemically unrelated to existing antiepileptics.

Public health relevance (burden of disease)

Epilepsy is a chronic disorder of the brain affecting both sexes and all ages; it is characterized by an enduring predisposition to epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.

Psychiatric and neurological disorders, including epilepsy, are among the most important contributors to the global burden of human suffering (*3*). Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally and a priority included in the WHO Mental Health Action Plan 2013–2020 (*4*).

Among 105 countries responding to a worldwide survey by WHO in collaboration with the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) within the framework of the Global Campaign Against Epilepsy, the mean number of people with epilepsy per 1000 population was 8.93 (SD 8.14; median 7.59) (*5*). Cumulative incidence (i.e. the lifetime probability of developing epilepsy) ranged between 3.1% and

5.8% (*6*). In developed countries, the age-specific incidence of epilepsy showed a U-shaped pattern, with higher rates for children and the elderly (over 65 years) than for adults; in developing countries, however, incidence peaks among children and young adults. This is probably the result of greater exposure to some preventable risk factors (e.g. perinatal risk factors, infections, traumas); it may also reflect a different structure of the populations at risk (i.e. a predominant distribution of young individuals and a short life expectancy). In most population-based prevalence and incidence surveys, no cause is found and diagnosis of the type of epilepsy remains difficult.

Epilepsy can be associated with significant morbidity due to the effects of seizures and/or treatment. It is associated with stigma and with psychological, social, cognitive and economic repercussions. People with epilepsy commonly encounter problems in: education; employment; driving; personal development; mental health; and social and personal relationships (*2*). It should also be noted that epilepsy may be the manifestation of an underlying pathology (e.g. stroke, tumour, cerebral palsy, infection).

Deaths related to epilepsy may be attributable to underlying disorders (causing a symptomatic epilepsy) or to the epilepsy itself, as in chronic epilepsy. Mortality among epileptic patients, measured as a standardized mortality ratio (SMR), is 2–3 times higher than in the general population in developed countries and as much as 6 times higher in developing countries (*7, 8*).

Diagnosis of epilepsy is primarily clinical and based on a detailed description of the events before, during and after a seizure given by the affected person and/or a witness. Seizures are generally described in two major groups – primary generalized seizures (including tonic–clonic seizures) and partial seizures. The availability of an antiepileptic agent with effectiveness in both types of seizures, and for paediatric as well as adult patients, would thus be a useful treatment option in clinical practice, since it could be offered to most people with epilepsy.

Summary of evidence – benefits (from the application)

The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs) to prevent the recurrence of epileptic seizures without adverse effects (*9*).

Given the wide variability in the frequency and severity of epileptic seizures, defining treatment success is not easy. The ILEA has defined treatment success as a seizure-free duration that is at least three times the longest seizure-free interval before the start of treatment, with a sustained response over 12 months (*10*).

Conversely, drug-resistant epilepsy is defined by ILAE as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”. No threshold relative to the frequency is mentioned, and a frequency of one seizure per year can therefore be regarded as treatment-resistant. “Treatment success can only be determined after the individual has remained without seizures for either 3 times the prior inter-seizure interval or 1 year, whichever is longer” (*10*).

Drug treatment of epilepsy is usually started as monotherapy; if the first AED is ineffective or not tolerated, a trial of a second AED is recommended. It is preferable for a patient to be

maintained on a single AED, since this increases the probability of compliance, provides a wider therapeutic index, and is more cost-effective than combination drug treatments. Combination therapy can be associated with drug interactions between AEDs, making it difficult to dose and monitor patients.

Assessing the place in therapy of anticonvulsants is challenging: most clinical trials compare the active treatment with placebo and therefore direct comparisons between them are not always available. The relative efficacy of new compounds must be inferred by means of systematic reviews and meta-analyses, but these methods do not provide conclusive evidence of differences in efficacy or tolerability.

The application searched for systematic reviews, randomized controlled trials (RCTs) not covered by the reviews, and guidelines, up to October 2016.

Systematic reviews and clinical trials considered patients affected by a variety of epileptic syndromes (new-onset generalized epilepsy, new-onset partial epilepsy, drug-resistant generalized epilepsy and drug-resistant partial epilepsy). RCTs were conducted in developed countries where the etiology of epilepsy and the characteristics of patients at risk are different from those in developing countries.

Lamotrigine as add-on (versus placebo) in drug-resistant epilepsy

Available evidence comes from RCTs testing the addition of lamotrigine to current therapy against addition of placebo. Specifically, in drug-resistant generalized epilepsy addition of lamotrigine to current anticonvulsant therapy was found to be "likely to be beneficial" (GRADE quality of evidence: moderate); it was superior to addition of placebo in reducing seizure frequency in three placebo-controlled RCTs (*11*). Studies included both adults and children but did not report outcomes separately. There was no meta-analysis of the three studies because of differences in study design. For patients with generalized tonic–clonic or absence seizures, adding lamotrigine significantly increased the proportion of those who experienced a 50% or greater reduction in seizure rate in all three RCTs. In the two RCTs that reported between-group comparisons, the proportion of people with at least a 50% reduction in seizure rate was clinically relevant. In one trial, over dose-escalation and maintenance phase, 64% achieved this seizure rate reduction with lamotrigine compared with 39% with placebo, $P < 0.05$; (intention-to-treat analysis) (*12*). In the second trial, a reduction in seizure rate of at least 50% was achieved in 75% of patients given lamotrigine compared with 32% given placebo, $P < 0.0001$ (*13*). A Cochrane review exploring the effectiveness of adjunctive lamotrigine for refractory primary generalized tonic¬–clonic seizures, and including two RCTs, found very similar results (*14*).

In drug-resistant focal epilepsy, a Cochrane systematic review found that addition of lamotrigine to current anticonvulsant therapy was superior to addition of placebo in reducing seizure frequency (GRADE quality of evidence: high). The review included 14 RCTs that involved both adults and children (38 infants, 199 children and 1721 adults) (*15*). The overall risk ratio (RR) for participants with 50% or greater reduction in seizure frequency was 1.80 (95% confidence interval (CI) 1.45–2.23) for 12 studies ($n = 1322$, adults and children), indicating that lamotrigine was significantly more effective than placebo in reducing seizure frequency in patients already on at least two seizure medications.

Lamotrigine versus other anticonvulsants as monotherapy

In monotherapy, available evidence comes from both head-to-head and placebo-controlled RCTs. One systematic review informing NICE (National Institute for Health and Care Excellence) guidelines (updated 2014) synthesized data from head-to-head RCTs and an individual patient data (IPD) meta-analysis testing lamotrigine versus other anticonvulsants in focal or generalized epilepsy (*2, 16*). Focal seizures data from direct and indirect comparisons show that lamotrigine and carbamazepine provided the best combination of seizure control and treatment failure. Lamotrigine was clinically superior to all other drugs for treatment failure but was less effective than carbamazepine in delaying time to first seizure (GRADE quality of evidence: low). Results for generalized epilepsy suggest that valproate might be the best choice: time to 12-month remission significantly favoured sodium valproate over lamotrigine monotherapy (hazard ratio (HR) 1.41; 95% CI 1.10–1.80) (moderate-quality evidence). These results overlap with the SANAD (Standard and New Antiepileptic Drugs) trial (*17*).

A Cochrane systematic review published in 2016 compared lamotrigine and carbamazepine; it included individuals with partial-onset seizures and showed mixed results. Carbamazepine was significantly better than lamotrigine for time to first seizure (hazard ratio (HR) 1.22; 95% CI 1.09–1.37) and for time to 6-month remission (HR 0.84; 95% CI 0.74–0.94), but there was a significant advantage for lamotrigine for withdrawal of allocated treatment (HR 0.72; 95% CI 0.63–0.82) (*18*). A network meta-analysis published in 2016 made multiple comparisons between AEDs and found that lamotrigine did not differ from other new AEDs (e.g. levetiracetam, oxcarbazepine, sultiam, topiramate) or from carbamazepine in terms of efficacy profile (*19*).

One subsequent RCT compared the effectiveness of valproate and lamotrigine in 60 newly diagnosed adults with idiopathic generalized tonic–clonic seizures. At the last observation, after 12 months' follow-up, 23 patients (76.67%) taking valproic acid and 17 (56.67%) taking lamotrigine were seizure-free. Statistical analyses were doubtful: re-analysis of data provided non-significant differences between groups (RR 1.22; 95% CI 0.86–1.73) (*20*). Another subsequent large RCT, which compared the effectiveness of lamotrigine with that of controlled-released carbamazepine and levetiracetam in 359 patients over 60 years of age with newly diagnosed focal epilepsy found that retention of lamotrigine was not significantly different between comparators, and seizure freedom rates at week 58 were no different across the groups (*21*).

Summary of evidence – harms (from the application)

Lamotrigine as add-on (versus placebo) in drug-resistant epilepsy

Cochrane reviews found that the addition of lamotrigine to current anticonvulsant therapy increased side-effects. The adverse events significantly associated with lamotrigine were: ataxia (RR 3.34; 99% CI 2.01–5.55; 12 RCTs; *n* = 1524); dizziness (RR 2.00; 99% CI 1.51–2.64; 13 RCTs; ***n*** = 1767); diplopia (RR 3.79; 99% CI 2.15–6.68; 3 RCTs; *n* = 943); and nausea (RR 1.81; 99% Cl 1.22–2.68; 12 RCTs; *n* = 1486) (***15***). In addition to these adverse events, another review found rash and headaches were also commonly reported. Skin reactions were confirmed by open-label studies, also in children (*22, 23*).

Lamotrigine versus other anticonvulsants as monotherapy

In monotherapy, a NICE systematic review (updated in 2014) showed that lamotrigine was better tolerated than carbamazepine, phenobarbital, gabapentin (except for skin rash) and topiramate (GRADE quality of evidence from very low to moderate) (*2*).

A Cochrane systematic review published in 2016 specifically compared lamotrigine and carbamazepine, mostly in individuals with partial-onset seizures, and showed a significant advantage for lamotrigine for time to withdrawal (HR 0.72; 95% CI 0.63–0.82; 9 RCTs; GRADE quality of evidence moderate) (*18*). This result was confirmed by a network meta-analysis of RCTs, published in 2016, which showed that lamotrigine was associated with fewer withdrawals due to adverse events than carbamazepine (OR 0.41; 95% CI 0.29–0.55) (*19*).

Other harms

Lamotrigine and other antiepileptic drugs have been associated with an increased risk of suicidal behaviour and ideation (*24).*

Lamotrigine during pregnancy

A Cochrane systematic review published in 2016 assessed congenital malformation outcomes in cases of monotherapy treatment of epilepsy in pregnancy. It included prospective cohort-controlled studies, cohort studies set within pregnancy registries and randomized controlled trials (*25*). Children exposed to lamotrigine in utero were not found to be at increased risk of major malformation compared with children born to women without epilepsy and to women with untreated epilepsy. As for drug–drug comparisons, children exposed to lamotrigine (LTG) were at lower risk than children exposed to valproic acid (VPA) (*n* = 4164 vs 2021; RR for VPA vs LTG 3.56; 95% CI 2.77–4.58), to carbamazepine (CBZ) (*n* = 4164 vs 3385; RR for CBZ vs LTG 1.34; 95% CI 1.01–1.76), to phenobarbital (PB) (*n* = 1959 vs 282; RR for PB vs LTG 3.13; 95% CI 1.64–5.88), to phenytoin (PHE) (*n* = 4082 vs 624; RR for PHE vs LTG 1.89; 95% CI 1.19–2.94) and to topiramate (TPM) (*n* = 3975 vs 473; RR for TPM vs LTG 1.79; 95% CI 1.06–2.94). These data are reassuring, showing that lamotrigine is safer than most other AEDs. Additionally, more observations are available for lamotrigine than for other AEDs: gabapentin, levetiracetam, oxcarbazepine, primidone and zonisamide were not associated with an increased risk, but there were substantially fewer data for these agents.

By contrast, children exposed to carbamazepine, phenytoin and valproic acid were at greater risk of malformation than children born to women without epilepsy or with untreated epilepsy. Similarly, children exposed to phenobarbital and topiramate were at greater risk of malformation than children born to women without epilepsy. For example, children exposed to valproic were at greater risk of malformation than children born to women without epilepsy (*n* = 467 vs 1936; RR 5.69; 95% CI 3.33–9.73) and those born to women with untreated epilepsy (*n* = 1923 vs 1259; RR 3.13; 95% CI 2.16–4.54).

A concurrent population-based case-malformed control study, based on 21 EUROCAT registries covering 10.1 million births in Europe (1995–2011) and a total of 226 806 babies with congenital anomalies, suggested that orofacial cleft (which had been previously hypothesized following a pooled analysis from five pregnancy registries including 1623 pregnancies) and other congenital anomalies – with the possible exception of clubfoot

(adjusted odds ratio (ORadj) 1.83; 95% CI 1.01–3.31) – were not significantly associated with lamotrigine monotherapy (*26*).

Lamotrigine in paediatrics

A systematic review of RCTs (*27*) assessed safety of lamotrigine in paediatric patients aged up to 18 years (78 articles involving 3783 paediatric patients; 2222 adverse events reported). Rash was the most commonly reported adverse event, occurring in 7.3% of the patients. Stevens–Johnson syndrome was reported rarely, with a risk of 0.09 per 100 patients. Treatment was discontinued in 72 children (1.9% of treated patients) because of an adverse drug reaction. These data are quite reassuring, although the possibility of Stevens–Johnson syndrome) should be carefully considered.

Persons with HIV/AIDS and epilepsy

The occurrence of seizure disorders is increased among people infected with HIV; incidence is about 6% (*28*). Clinically significant drug interactions can occur when antiretroviral agents are combined with enzyme-inducing AEDs such as carbamazepine, phenytoin and phenobarbital. Such interactions may result in altered serum levels of both AEDs and antiretrovirals and can lead to higher rates of HIV treatment failure compared with use of antiretroviral agents with non-enzyme-inducing AEDs. In persons with HIV/AIDS treated with antiretroviral agents, the use of non-enzyme-inducing anticonvulsants (such as lamotrigine and other "newer" AEDs) is preferable (*29, 30*).

Drug safety alert

A drug safety alert has been issued by the FDA on the risk of aseptic meningitis associated with lamotrigine. A total of 40 cases of aseptic meningitis in adults and paediatric patients taking lamotrigine were reported from 1994 to 2009; more than 46 million prescriptions were dispensed over that period (*31*).

Additional evidence (not in the application)

N/A

WHO guidelines

Lamotrigine is included in WHO's 2015 *Update of the Mental Health Gap Action Programme (mhGAP) guidelines for mental, neurological and substance use disorders* as a recommended option for add-on therapy in patients with medication-resistant convulsive epilepsy (conditional recommendation, moderate-quality evidence) (*32*).

Costs/Cost–effectiveness

In developed countries, the price of antiepileptics varies considerably. Branded drugs are generally more expensive. According to data from HAI (National Price Sources of Health Action International), the cost per defined daily dose (DDD) of lamotrigine is higher of that of phenobarbital but comparable to that of carbamazepine.

Based on a cost–effectiveness analysis, the NICE guideline published in 2012 (updated February 2016) (*2*) recommended the following as cost-effective treatments for the United Kingdom National Health Service (NHS):

- lamotrigine and oxcarbazepine for adjunctive treatment in children, young people and adults with refractory focal seizures;
- lamotrigine for newly diagnosed focal seizures requiring treatment;
- lamotrigine, with the lowest total cost, is likely to be cost-effective for first-line treatment in children, young people and adults with newly diagnosed generalized tonic–clonic seizures.

Considering that no other relevant comparative economic evidence was found, and although they refer to the NHS, these analyses suggest that lamotrigine may be a cost-effective anticonvulsant drug in different clinical scenarios compared with the available alternatives.

Availability

Lamotrigine was approved by the FDA in 1994 for use in partial-onset seizures. It was ultimately approved for monotherapy in 1998.

Lamotrigine as monotherapy in generalized seizures has been licensed by the EMA but not the FDA.

Other considerations

Topiramate and lamotrigine are the two AEDs with the broadest indications, both in paediatric and adult populations.

	Authorized indications – lamotrigine (EMA, FDA)			
	Monotherapy		*Adjunctive therapy*	
	Generalized	Partial	Generalized	Partial
EMA	A, Ad ≥13 y	A; Ad ≥13 y	A, Ad, C ≥2 y	A, Ad, C ≥2 y
FDA	NO	A, Ad ≥16 y*	A, Ad, C ≥2 y	A, Ad, C ≥2 y

A = adults; Ad = adolescents; C = children; y = years of age

* Conversion to monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone or valproate as the single AED.

Committee recommendations

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

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.

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Section 6: Anti-infective medicines

6.1: Anthelminthics

6.1.1: Intestinal anthelminthics

Ivermectin – change: new indication – EML and EMLc

Ivermectin **ATC Code: P02CF01**

Proposal

The application proposed inclusion of ivermectin on the EML and EMLc for use as an intestinal anthelminthic against *Strongyloides stercoralis*, and in combination with albendazole against soil-transmitted helminthiasis (STH).

The goal for the addition of ivermectin to the EML and EMLc for strongyloidiasis is predominantly one of clinical use: currently there are no large-scale public health deworming programmes for this disease. STH infections are treated both clinically and with preventive chemotherapy in large-scale "mass drug administration" programmes.

Applicant(s)

Dr Antonio Montresor

WHO technical department

Department of Control of Neglected Tropical Diseases

EML/EMLc

EML and EMLc

Section

6.1.1 Intestinal anthelminthics

Dose form(s) and strength(s)

Tablet (scored): 3 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Currently, the EML and EMLc include ivermectin 3-mg scored tablet as an antifilarial (Section 6.1.2).

Public health relevance (burden of disease)

Target 3.3 of the Sustainable Development Goals is to end, by 2030, the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and to combat hepatitis, waterborne diseases and other communicable diseases.

Strongyloidiasis

Strongyloidiasis is globally distributed and is endemic in the tropics and subtropics (*1, 2*). An estimated 30–100 million people are infected worldwide; there are no precise data on prevalence in endemic countries.

In low- and middle-income countries, strongyloidiasis is endemic; children are at highest risk of chronic infection. Parasitic worm infections are associated with malnutrition and, in children, with impaired growth and cognitive development and poor school performance. Heavy worm infection in children is associated with anaemia.

Soil-transmitted helminthiasis

The global target is to eliminate morbidity due to STH in children by 2020. This will be achieved by treating at least 75% of children (an estimated 873 million) in endemic areas (*3*).

The STH disease cluster is considered to be the most widespread of the neglected tropical diseases worldwide. The most recent estimates indicate that close to 1.5 billion people are infected with *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Necator americanus* and/or *Ancylostoma duodenale* (hookworms) in more than 100 endemic countries (*4, 5*). Some 3.3 million disability-adjusted life years (DALYs), resulting from symptomatic infection, wasting, mild abdominopelvic problems and anaemia, are attributed to STH infection (*4, 6*). The highest risk groups are children, who are in a critical phase of growth and development, and women of childbearing age, including pregnant women, who have increased nutritional requirements during pregnancy and lactation (*7*).

Summary of evidence – benefits (from the application)

Strongyloidiasis

The application presented the results of a 2016 Cochrane systematic review (*8*) that included four studies comparing ivermectin with albendazole. Two of the four studies included adults and children (*9, 10*). The results showed that parasitological cure was higher with ivermectin (risk ratio (RR) 1.79; 95% confidence interval (CI) 1.55–2.08; 478 participants; moderate-quality evidence – downgraded for risk of bias (two trials did not use allocation concealment and no description of allocation method was provided)).

In the same review, three trials compared ivermectin with tiabendazole. The results showed little difference in parasitological cure (RR 1.07; 95% CI 0.96–1.20; 467 participants; low-quality evidence). The review found that single-dose ivermectin (200 µg/kg) was

associated with the same rate of parasitological cure as two-dose ivermectin treatment (RR 1.02; 95% CI 0.94–1.11). However, it noted that this result was based on only two trials with a small number of participants (*n* = 94).

Soil-transmitted helminthiasis

The application presented data for the efficacy of ivermectin alone and co-administered with albendazole against soil-transmitted helminths from eight randomized controlled trials identified by literature search (*9, 11–16*). Cure rates (CRs) and egg reduction rates (ERRs, when available) were extracted for each treatment against *A. lumbricoides, T. trichiura* and hookworms. Notably, not all studies evaluated efficacy of the drugs against all STHs.

Belizario et al. (*11*) and Knopp et al. (*13*) reported that albendazole–ivermectin is not more effective at eliminating *A. lumbricoides* than albendazole alone. These two studies revealed a CR of 79.8% against *A. lumbricoides* infections for the albendazole–ivermectin combination versus 73.5% for albendazole alone. In terms of intensity, they observed ERRs of 100% and 99.9% for the co-administration versus 99.9% and 100% for albendazole alone.

Meta-analysis of three studies (*11–13*) which compared albendazole–ivermectin with albendazole alone including 342 patients revealed co-administration of albendazole–ivermectin to be more effective at eliminating *T. trichiura* infection than albendazole alone (CR 47%, RR 0.53; 95% CI 0.3–0.76). In these studies, ERR ranged from 91.3% to 99.7% for albendazole–ivermectin and from 40.3% to 97.2% for albendazole alone.

One study evaluated the efficacy of albendazole–ivermectin against hookworm infections (*13*). The results indicated that the combination is more effective in curing hookworms than albendazole alone. The difference in ERRs, however, was small – 95.9% with the combination and 94% with albendazole alone.

Four other studies compared the efficacy of ivermectin alone against *T. trichiura* (CR 52.7%; ERR from 58.9–98.2%) (*11, 15-17*); *A. lumbricoides* (CR 90.3%; ERR 100%) (*11, 15, 16*); and hookworms (CR: 24.6%; ERR reported in one study as 80%) (*15–17*).

The application concluded that the evidence showed ivermectin to be a highly efficacious treatment for strongyloidiasis, with greater efficacy than albendazole, mebendazole and tiabendazole and increased efficacy in children under 5 years of age. For STH, the application stated that ivermectin administered with albendazole is more efficacious than albendazole alone in treating *T. trichiura*; for treatment of *A. lumbricoides* and hookworm, treatment with the combination is largely comparable to albendazole alone.

Summary of evidence – harms (from the application)

Strongyloidiasis

In the four studies comparing ivermectin with albendazole included in the Cochrane systematic review (*8*), there were no statistically significant differences in adverse events (RR 0.80; 95% CI 0.59–1.09; 518 participants; low-quality evidence). In the three trials comparing ivermectin with tiabendazole, adverse events were less common with ivermectin (RR 0.31; 95% CI 0.20–0.50; 507 participants; moderate-quality evidence). Dizziness, nausea and disorientation were commonly reported in all drug groups. There

were no reports of serious adverse events.

Zaha et al. (*18*) found significant liver abnormalities in two ivermectin dosage groups. In the 110µg group, a rise in glutamic pyruvic transaminase (GPT) or glutamic oxaloacetic transaminase (GOT) was observed in 6.9% (19/274) of the patients whose liver function was normal before treatment. In the 200-µg group, liver dysfunction was observed in 6.5% (6/92) of patients. The abnormalities in both groups were mild, transient and not clinically important.

Soil-transmitted helminthiasis

Four studies compared the safety of co-administered albendazole–ivermectin with that of albendazole alone (*13, 19–21*). Co-administration was associated with more adverse events than either albendazole or ivermectin alone; this was not significant in either case (*19, 20*).

The frequency and severity of adverse events have been shown to be associated with baseline infection status, intensity of infection and infection-related immune response parameters. For example, when administered to subjects with high *Loa loa* microfilaraemia, ivermectin has been associated with severe adverse reactions such as neurological signs, encephalopathy and coma (*22*). In case of confirmed loiasis hyper-endemicity, alternative treatment schemes should be considered.

Of a total of 1656 reports for ivermectin in VigiBase, 525 (31.7%) – mostly (397) from Sierra Leone – contained both ivermectin and albendazole. Between 2007 and 2015, more than 33 million tablets of ivermectin have been administered with albendazole in the lymphatic filariasis programme, giving rise to approximately 11 adverse events per one million treatments during that period. All reported adverse events were considered minor.

The most commonly reported adverse reaction for ivermectin alone or with albendazole were pruritus, headache, dizziness, vomiting, urticarial rash and diarrhoea. In total, there were 459 reports of ivermectin having caused a serious adverse reaction; there were 63 deaths (probably due to causes other than ivermectin itself). Concomitant medication was frequently administered. The most frequent adverse reaction reported in cases that resulted in death included strongyloidiasis, drug ineffectiveness, pneumonia, pyrexia, multiple organ dysfunction syndrome, acute respiratory distress syndrome, cardiac arrest, septic shock, Stevens–Johnson syndrome, thrombocytopenia and toxic epidermal necrolysis. Full assessment of the health status of individuals before treatment to exclude seriously ill individuals is recommended (*7*).

It is recommended that ivermectin not be administered to children less than 90 cm tall or weighing less than 15 kg, pregnant women, lactating women in the first week after birth or severely ill individuals.

Additional evidence (not in the application)

N/A

WHO guidelines

WHO's *Preventive chemotherapy in human helminthiasis. Coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers* recommends ivermectin and albendazole as treatment options for strongyloidiasis.

Ivermectin is not currently among the recommended medicines (albendazole or mebendazole) for treatment of STH (*7*).

Costs/Cost–effectiveness

According to the MSH (Management Sciences for Health) *International Medical Products Price Guide* in 2013, the median buyer price per 3-mg tablet of ivermectin was US$ 0.0296 (*23*).

For large-scale treatment of STH infection, the application asserted that adding ivermectin to albendazole that is already being delivered for mass drug administration programmes would involve only marginally increased costs, namely those associated with ivermectin purchase, and would have ancillary benefits for strongyloidiasis in co-endemic areas.

Availability

Ivermectin has wide market availability.

Ivermectin 3-mg tablet was included on the Invitation for Expression of Interest for WHO prequalification in July 2015. The product is not currently prequalified.

Other considerations

N/A

Committee recommendations

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.

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6.2: Antibacterials

6.2.1: Beta-lactam medicines
6.2.2: Other antibacterials
Comprehensive review of antibiotics – EML and EMLc
Overview

The comprehensive review of antibiotics in sections 6.2.1 and 6.2.2 of the EML and EMLc by the Expert Committee was informed by three applications.

- A review of antibiotics for 21 priority infectious syndromes in adults and children was conducted by the Department of Health Research Methods, Evidence and Impact, McMaster University, Canada (the McMaster Group):
  community-acquired pneumonia
  pharyngitis
  sinusitis
  otitis media
  hospital-acquired pneumonia
  ventilator-associated pneumonia
  sepsis in children
  urinary tract infection (UTI)
  catheter-associated UTI
  endocarditis
  meningitis
  central-line infections
  complicated intra-abdominal infections
  wound, skin and soft-tissue infections
  surgical site infections
  cellulitis
  acute infectious diarrhoea
  sexually transmitted infections
  exacerbations of chronic obstructive pulmonary disease
  bone and joint infections
  febrile neutropenia

- A review of antibiotics for five specific bacterial infections in children, based on a review of WHO guidelines, was conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health:
  community-acquired pneumonia
  sepsis
  dysentery
  cholera
  severe acute malnutrition

- A review of antibiotics for specific sexually transmitted infections, based on a

review of updated WHO guidelines, was conducted by the WHO Department of Reproductive Health and Research:
Neisseria gonorrhoeae
Treponema pallidum (syphilis)
Chlamydia trachomatis

The Expert Committee appreciated the comprehensive review submitted by the McMaster Group, which formed the basis for the selection of antibiotics for the updated EML and EMLc. It was noted, however, that the methodology – based on published systematic reviews and higher quality guidelines – provided limited information on antibiotic selection in the low- and middle-income country (LMIC) setting.

The Expert Committee included clinical infection syndromes requiring antibiotics that are commonly encountered globally. The main focus was on empirical treatment choices for important (mostly) community-acquired infections that are broadly applicable in most countries. Surgical prophylaxis, was not considered as a part of this review because it is the subject of a WHO guideline being developed by the department of Service Delivery and Safety.

The recommendations for the Model Lists are not guidelines, and the recommended empirical treatment choices will be influenced by local/national specificities, such as the availability of antibiotics and local resistance patterns; they may also not apply to a specific patient and should not replace clinical judgment. As a general rule, alternatives for use in case of allergy were not considered by the Expert Committee when discussing first- and second-choice medicines for each syndrome.

Severity of infection was considered when relevant, to differentiate choices and help optimize antibiotic selection.

Guiding principles for antibiotic categorization

The Expert Committee noted that the prescription of any antibiotics must balance the benefits and risks to patients with the impact on public health.

The terms “core” and “targeted”, used in the application from the McMaster Group, were changed, because: “core” already has a definite meaning in the context of the EML/EMLc (core and Complementary Lists); and, in the context of infectious diseases, “targeted” means based on microbiology results.

Empirical therapy for each clinical infection syndrome includes first- and second-choice antibiotics. First-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents with positive benefit–risk ratios and low resistance potential. Second-choice antibiotics are more broad-spectrum agents with a less favourable benefit–risk ratio and higher resistance potential.

First- and second-choice antibiotics were aligned to recent WHO guidelines on sexually transmitted infections (STIs; gonorrhoea, syphilis, chlamydia) and five paediatric syndrome reviews (community-acquired pneumonia, neonatal sepsis, cholera, dysentery and severe acute malnutrition). All first- and second-choice antibiotics are listed in the EML(c), each with the recommended indications.

To improve both access and clinical outcomes, the Expert Committee designated antibiotics that are first- or second-choice antibiotics in at least one syndrome as key “Access” antibiotics

emphasizing their role as the antibiotics that should be widely available, affordable and quality-assured.

Access group antibiotics

In the lists that follow, antibiotics shown in italics appear on the Complementary List; those marked with an asterisk are Watch group antibiotics, included in the EML/EMLc only for specific, limited indications.

6.2.1: Beta-lactam medicines	***6.2.2: Other antibacterials***
amoxicillin	amikacin
amoxicillin + clavulanic acid	azithromycin*
ampicillin	chloramphenicol
benzathine benzylpenicillin	ciprofloxacin*
benzylpenicillin	clarithromycin*
cefalexin	clindamycin
cefazolin	doxycycline
cefixime*	gentamicin
cefotaxime*	metronidazole
ceftriaxone*	nitrofurantoin
clozacillin	spectinomycin (EML only)
phenozymethylpenicillin	sulfamethoxazole + trimethoprim
piperacillin + tazobactam*	vancomycin (oral)
procaine benzylpenicillin	*ancomycin (parenteral)*
*meropenem**	

For clarity and cross-referencing purposes, the Expert Committee also wished to encourage the general principles of antibiotic stewardship in all sectors, building on and reflecting the important work done in designating the WHO *List of critically important antimicrobials for human medicine* (CIA List) (*1*), which aims at preserving medically important antimicrobials used in food animal production. The intent and purpose of the EML and EMLc include factors other than those considered by the CIA List: while the EML and EMLc take into account bacterial resistance, they also include issues of efficacy and access. The purpose of the CIA List was to assess the impact of resistance as well as the risk of transmission through the food chain. Thus, while there is relevant overlap between the EML Watch group and highest-priority agents on the CIA list (see below), there will also be inevitable differences, including the names of antibiotic groupings.

To assist in the development of tools for antibiotic stewardship at local, national and global levels, the Expert Committee developed two stewardship groups of antibiotics based on their probability of selecting resistance. The larger "Watch" group and a more focused "Reserve" group may be valuable for such activities as local, national and global monitoring of use, development of guidelines and educational activities.

Watch group antibiotics

The stewardship Watch group includes antibiotic classes that are generally considered to have higher resistance potential and that are still recommended as first- or second-choice treatments but for a limited number of indications. These medicines should be prioritized as key targets of

local and national stewardship programmes and monitoring. The group includes the highest-priority agents on the CIA List (*1*) and/or antibiotics that are at relatively high risk of selection of bacterial resistance. The CIA List ranks antimicrobials according to their relative importance in human medicine and can be used in the development of risk management strategies for the use of antimicrobials in food production animals.
Seven pharmacological classes were identified for this group. As noted above, monitoring systems should be in place to ensure that their use is in line with recommended indications.

Quinolones and fluoroquinolones: e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
These antibiotics are considered highest-priority critically important antimicrobials on the CIA List and carry a high risk of selection of bacterial resistance (in particular methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamases (ESBL), and resistance to fluoroquinolones).
Ciprofloxacin is listed on the EML/EMLc as a first-choice option for acute invasive bacterial diarrhoea/dysentery, low-risk febrile neutropenia, pyelonephritis and prostatitis (mild to moderate), and as a second-choice option for cholera and complicated intraabdominal infections (mild to moderate).

3rd-generation cephalosporins (with or without beta-lactamas inhibitor): e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime
These antibiotics are considered highest-priority critically important antimicrobials on the CIA List and carry a high risk of selection of bacterial resistance (in particular ESBL).
Ceftriaxone is listed on the EML/EMLc as a first-choice option for acute bacterial meningitis, community-acquired pneumonia (severe), complicated intra-abdominal infections (mild, moderate and severe), hospital-acquired pneumonia, *Neisseria gonorrhoeae*, pyelonephritis and prostatitis (severe), and as a second-choice option for acute invasive bacterial diarrhoea/dysentery, bone and joint infections, pyelonephritis or prostatitis (mild to moderate), and sepsis in neonates and children.
Cefotaxime is listed on the EML/EMLc for the same indications as ceftriaxone with the exceptions of *Neisseria gonorrhoeae* and acute invasive bacterial diarrhoea/dysentery.
Cefixime is listed as a second-choice option for acute invasive bacterial diarrhoea/dysentery and *Neisseria gonorrhoeae*.

Macrolides: e.g. azithromycin, clarithromycin, erythromycin
These antibiotics are considered highest-priority critically important antimicrobials on the CIA List and carry a high risk of selection of bacterial resistance (particularly resistance to macrolides). With its remarkably long half-life, azithromycin carries the highest risk of resistance among the macrolides.
Azithromycin is listed on the EML/EMLc as a first-choice option for trachoma, yaws, *Chlamydia trachomatis*, cholera and *Neisseria gonorrhoeae*, and as a second-choice option for acute invasive bacterial diarrhoea/dysentery and Neisseria gonorrhoeae.
Clarithromycin is listed as a first-choice option for *Helicobacter pylori* and community-acquired pneumonia (severe), and as a second-choice option for pharyngitis.

Glycopeptides: e.g. teicoplanin, vancomycin
These antibiotics are considered highest-priority critically important antimicrobials on the

CIA List and carry a high risk of selection of bacterial resistance (e.g. vancomycin-resistant enterococci (VRE)).
Vancomycin is listed on the EML/EMLc as a second-choice option for *Clostridium difficile* infections and high-risk febrile neutropenia.

Antipseudomonal penicillins with beta-lactamas inhibitor: e.g. piperacillin + tazobactam
These antibiotics have a broad spectrum of activity and carry a high risk of selection of bacterial resistance.
Piperacillin + tazobactam is listed on the EML/EMLc as a first-choice option for complicated intra-abdominal infections (severe), high-risk febrile neutropenia and hospital-acquired pneumonia.

Carbapenems: e.g. meropenem, imipenem + cilastin
Carbapenems have a broad spectrum of activity and their use should be limited to a small number of specific indications. Overuse of carbapenems has been associated with increasing prevalence of infections due to resistant organisms (e.g. MRSA, VRE).
Meropenem is listed on the EML and EMLc as second-choice treatment for acute bacterial meningitis in neonates, complicated severe intra-abdominal infections and high-risk febrile neutropenia. *Imipenem + cilastatin* is an alternative in some cases.

Penems: e.g. faropenem
No penems are included on the EML or EMLc.

Reserve group antibiotics

The more focused stewardship "Reserve" group includes antibiotics and antibiotic classes on the basis of their "last resort" status (antibiotics or antibiotic classes to be used when other alternatives would be inadequate or have already failed, e.g. in serious life-threatening infections due to multidrug-resistant bacteria)). This group was identified to improve targeted access according to available recommendations and to reduce the risk of development of resistance to these agents. They should be protected and prioritized as key targets of high-intensity national and international stewardship programmes involving monitoring and utilization reporting, to preserve their effectiveness. Eight antibiotics or antibiotic classes were identified for this group:

aztreonam
4th-generation cephalosporins, e.g. cefepime
5th-generation cephalosporins, e.g. ceftaroline
polymyxins, e.g. poymyxin B, colistin
fosfomycin (IV)
oxazolidinones, e.g. linezolid
tigecycline
daptomycin

Other considerations

The Expert Committee noted that there remain many barriers to reducing broad-spectrum antibiotic use. For example, the Committee noted that allergy skin testing of all patients

before penicillin use is required in some regions and recommended strongly against this as a routine practice. It is unnecessary and drives the use of broader-spectrum antibiotics such as cephalosporins and macrolides, leading to increased levels of bacterial resistance.

The Expert Committee noted that sustained availability of the key antibiotics in the Access group remains a major concern in countries of all income levels. Regular and prolonged shortages of antibiotics on the Access list are a threat to responsible antibiotic use, forcing clinicians to use broader-spectrum antibiotics that are sometimes less efficacious and more toxic for patients.

The Expert Committee noted that major concerns remain about substandard and counterfeit medicines within the key Access group of antibiotics.

The Expert Committee noted the development of the key principles of access and stewardship:

- Antibiotic stewardship is a strategy aimed at ensuring that antibiotics are used responsibly. Responsible use is a balance between best efficacy for the patient and minimization of the risk of adverse effects, both for the individual patient (classical adverse events, *C. difficile* infections, bacterial resistance) and for the population (bacterial resistance).
- Antibiotic stewardship is a behaviour change strategy and thus a complex and health system-wide intervention. Antibiotic stewardship programmes should use a combination of several interventions, in all settings (primary care, hospitals) and at all levels (local, national, international), adapted to the local context. A single intervention is not enough. These programmes can have a positive impact provided that sufficient resources are made available and are sustainable and that there is strong political and institutional support. However, disseminating recommendations at local or national level is not enough, and a detailed and long-term implementation plan must be rolled out in order to effect change. Long-term monitoring of indicators is critical to assess the impact of the stewardship programme and to adapt it when necessary.
- Antibiotic use is a complex interplay between patients, prescribers and non-prescriber health-care professionals, all influenced by their environment (system organization, culture, regulation). An antibiotic stewardship programme must target the general public, health-care professionals (whether they prescribe or not) and policy-makers. It must try to change behaviour – a notoriously difficult process – by acting at the level of both the individual and the system. The following are examples of the many behavioural interventions that can be used:
  - system change: having antimicrobial stewardship teams as a mandatory requirement in hospitals, or banning over-the-counter sale of antibiotics by law;
  - targeting the general public: awareness campaigns;
  - targeting prescribers: education, audits and feedback, promoting the use of guidelines (merely making guidelines available will not lead to a change in

prescribing).

- The Expert Committee encouraged regular monitoring of the availability of the key Access antibiotics of the EML and EMLc. Monitoring systems will also be useful for the Watch group and applied more rigorously for the Reserve group, to capture data on actual versus optimal use.
- The Expert Committee noted the need for further work to develop and expand the key principles of access and stewardship; it recommended the appointment of a standing EML Antibiotics Working Group to:
  - consider reviewing additional clinical syndromes not included in the current update, e.g. typhoid fever, medical and surgical prophylaxis, dental infections, acute undifferentiated fever;
  - work on the current clinical synopsis reviews, adapting them into shorter structured documents;
  - coordinate the development of a guidance document on optimal dose and duration of antibiotic treatments to maximize clinical efficacy while minimizing the selection of resistance;
  - review the differential effect of antibiotic classes on the selection of resistance;
  - relate the work of the EML and EMLc to the future essential in-vitro diagnostics list, which should include work on diagnostics related to antimicrobial resistance as soon as feasible;
  - propose improved methods for defining and communicating the key stewardship messages associated with the new categorization and develop more detailed guidance to assist with the implementation of recommendations in national programmes.
  - investigating, or making an inventory of, key older antibiotics that may be considered important to add to the Reserve group.

Reference

1. WHO Advisory Group on Integrated Surveillance of Antimicrogial Resistance (AGISAR). Critically important antimicrobials for human medicine, fourth revision 2013. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1, accessed 21 March 2017).

Community-acquired pneumonia (CAP)

Applicant(s)

McMaster Group

WHO Department of Maternal, Newborn, Child and Adolescent Health

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Introduction

(description of the condition/infecting organisms/public health need)

Community-acquired pneumonia (CAP) refers to pneumonia that is acquired in the community rather than within the health-care system. Patients of advanced age or with comorbid conditions or greater severity of illness are more likely to be hospitalized. Although there is consensus that *Streptococcus pneumoniae* is the most common bacterial cause of CAP, the need for so-called "atypical coverage" of pathogens such as *Chlamydia pneumoniae*, *Mycoplasma* or *Legionella* with antibiotics such as macrolides or fluoroquinolones has been controversial. The emergence of macrolide and fluoroquinolone resistance in the community has created concern, and the need for these medicines in addition to antibiotics with antipneumococcal coverage has been debated.

The following summary considers the CAP syndrome review conducted by the McMaster Group, and the review of CAP guidelines for paediatrics conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.

Summary of evidence (from the application)

Adult outpatient therapy

A 2014 Cochrane review covering 11 randomized controlled trials (RCTs) of 3352 participants older than 12 years with a diagnosis of CAP reported that, for outpatients, there was no advantage of one antibiotic over another for efficacy when the comparison was either between fluoroquinolones and macrolides or between different macrolides (*1*). However, there were substantially fewer adverse events with clarithromycin than with erythromycin (odds ratio (OR) 0.3; 95% confidence interval (CI) 0.2–0.46). The application therefore did not propose erythromycin for inclusion on the EML for this indication.

Among 423 patients, substantially more experienced adverse events with azithromycin (42/211) than with levofloxacin (26/212) (OR 1.78; 95% CI 1.04 to 3.03) (*1*). Although adverse events such as nausea and vomiting are not in themselves life-threatening, they can have an important impact on adherence. There was no comparison of clarithromycin with levofloxacin. Given these adverse effects, and the fact that the U.S. Food & Drug Administration (FDA) has warned about fatal cardiovascular events (*2*), the application did not propose azithromycin for inclusion on the EML for this indication.

A review of 16 RCTs (4989 patients), which mostly assessed outpatients with mild to moderate CAP, found no difference in mortality between those treated with macrolides and those given fluoroquinolones (risk ratio (RR) 1.03: 95% CI 0.63–1.68), although gastrointestinal adverse events were more common with macrolides (*3*). The wide confidence intervals do not exclude a clinically important effect, however, and the findings therefore do not help in differentiating between these antibiotic classes.

Adult inpatient therapy

The severity of illness and concerns about complications mean that the approach to hospitalized patients differs from that to outpatients. Coverage for atypical pathogens has been a source of controversy.

A 2012 Cochrane review (28 RCTs; 5939 participants) of empirical therapy for CAP in hospitalized adults showed that atypical coverage offered no additional benefit compared with typical coverage in reducing deaths (*4*): there was no difference between groups for mortality (RR 1.14; 95% CI 0.84–1.55). However, only one study compared a beta-lactam with a beta-lactam plus a macrolide. The width of the confidence intervals exceeds that specified by the applicants for similarity (i.e. within 5%) and these results therefore do not contribute to antibiotic selection. Although there was no difference in overall adverse events between the groups, gastrointestinal events were less common in the atypical group (RR 0.70; 95% CI 0.53–0.92).

A 2015 review (16 RCTs; 4809 participants) reported no difference in mortality between fluoroquinolones and beta-lactam/macrolide combinations (RR 0.99; 95% CI 0.70–1.40), but wide confidence intervals limited inferences (*5*). However, a reduction in clinical failure with fluoroquinolones was reported (RR 0.72; 95% CI 0.57–0.91). Overall, while these findings may be useful in helping clinicians to select antibiotics, the large number of antibiotics being compared was not considered by the applicants to be helpful for informing selection of antibiotics for the EML.

The lack of additional benefit of atypical antimicrobials in patients with CAP with mild to moderate illness was also demonstrated in a recent non-inferiority cluster RCT (*6*). The trial randomized patients to beta-lactams, a combination of beta-lactams and atypical antibiotics, or to fluoroquinolones. The 90-day mortality was 9.0%, 11.1% and 8.8%, respectively. Compared to the beta-lactam strategy, the risk differences (RD) for 90-day mortality were 1.9% (90% CI −0.6 to 4.4) with the beta-lactam/macrolide strategy and –0.6% (90% CI −2.8 to 1.9) with the fluoroquinolone strategy. The results indicated non-inferiority of the beta-lactam strategy. These data are of particular relevance, because it does not appear that adding atypical antibiotics to beta-lactam antibiotics makes a clinically important difference, at least for patients presenting with mild to moderate CAP.

Whether atypical coverage is required for CAP has been an important concern; another question is whether there is a difference between fluoroquinolones and macrolides. A review of five RCTs for inpatients addressed this question and reported no difference between fluoroquinolones and macrolides for mortality (RR 1.13; 95% CI 0. 65–1.98) (*7*). The confidence intervals are relatively wide and the results do not allow either protection or harm from fluoroquinolones compared with macrolides to be inferred.

Children

A 2013 Cochrane review of antibiotics within an outpatient or hospital setting (29 RCTs; 14 188 children) showed that cure rates with amoxicillin were similar to those with sulfamethoxazole + trimethoprim (SMX–TMP) (odds ratio (OR) 1.03; 95% CI 0.56–1.89) (*8*). In this review, "cure" referred to an absence of symptoms at the end of treatment, "failure" was the presence of a sign at the end of treatment, and "relapse" was defined as recurrence of disease in follow-up of a patient after cure. Given the wide confidence intervals (i.e. >10%),

these data were not considered by the applicants to inform the proposal of antibiotics for the EML. Amoxicillin resulted in better cure rates than amoxicillin + clavulanic acid (RR 10.44; 95% CI 0.29–38.2), suggesting that amoxicillin alone may be preferred. Failure rate at 21 days was greater for chloramphenicol compared with ampicillin and gentamicin (OR 1.43; 95% CI 1.03–1.98). The applicants considered that this important evidence supported non-inclusion of chloramphenicol on the EML and inclusion of ampicillin and gentamicin. Cure rate was significantly greater for amoxicillin compared with cefpodoxime (OR 0.20; 95% CI 0.08–0.53), which argues for the inclusion of amoxicillin and against the inclusion of oral third-generation cephalosporins on the EML.

Another systematic review examined antibiotic therapy for pneumonia in children in low- and middle-income countries. The pooled estimate of two studies involving children with very severe pneumonia showed no significant decrease in death rates between ampicillin and gentamicin compared with chloramphenicol (RR 0.71; 95% CI 0.51–1.00) (*9*). The failure rate, however, was lower with ampicillin and gentamicin compared with chloramphenicol (RR 0.79; 95% CI 0. 66–0.94). On this basis, and because of its potential toxicity, chloramphenicol was not proposed by the applicants for inclusion on the EML. When SMX–TMP was compared with amoxicillin, failure rates were higher for SMX–TMP (RR 1.79; 95% CI 1.13–2.84).

For non-severe pneumonia, there was no difference between SMX–TMP and amoxicillin for cure rate in two RCTs (3468 children; RR 0.99; 95% CI 0.96–1.01) (*10*). That amoxicillin is better tolerated, with fewer side-effects, than SMX–TMP argues in favour of including amoxicillin alone on the list.

Overall, these data point to beta-lactam regimens as being a key part of therapy for CAP in children, which is similar to what existing evidence suggests for adults.

As noted, the systematic reviews that were identified provided limited information on superiority. Most of the RCTs included in the reviews were non-inferiority studies but frequently did not meet the criteria for non-inferiority determined by the applicants. The RCTs did not show mortality benefit of adding a fluoroquinolone or macrolide to a beta-lactam compared with beta-lactam monotherapy. In children, amoxicillin appeared to be either equivalent to, or have better cure rates than, SMX–TMP. The greater tolerability of amoxicillin means it is preferred. Better cure rates were achieved with amoxicillin than with cefpodoxime, and there were fewer clinical failures with ampicillin and gentamicin than with chloramphenicol, making these antibiotics the preferred choices.

Guidelines (from the application)

Guidelines of the British Thoracic Society (BTS) (*26*) and the Infectious Diseases Society of America (IDSA) for adults were summarized in the application. Currently available IDSA guidelines (which are being updated) include use of macrolides (either alone or in combination), respiratory fluoroquinolones, beta-lactams (cefotaxime, ceftriaxone, or ampicillin + sulbactam); use of antipseudomonal antibiotics when needed (piperacillin + tazobactam) or carbapenems (imipenem or meropenem); or use of an aminoglycoside. BTS recommendations include a single antibiotic, a combination of amoxicillin and macrolide, beta-lactam/beta-lactamase-inhibitor combinations and a macrolide, depending on severity of illness.

For children, IDSA guidelines include amoxicillin, macrolides for outpatients and ampicillin or penicillin G (benzylpenicillin), ceftriaxone or cefotaxime, or a combination of macrolide and a beta-lactam (*11*). Vancomycin is recommended if methicillin-resistant *Staphylococcus aureus* (MRSA) is being considered. The guidelines also recommend doxycycline as an alternative first-line to macrolides as well as ceftriaxone or ampicillin + sulbactam for patients in intensive care. The BTS guidelines recommend amoxicillin as first choice for oral antibiotic therapy in children and propose amoxicillin + clavulanic acid, cefaclor, erythromycin, azithromycin and clarithromycin as alternatives (*12*). They suggest that macrolide antibiotics may be added at any age if there is no response to first-line empirical therapy or if either *Mycoplasma* or *Chlamydia* pneumonia is suspected or in very severe disease. They recommend amoxicillin + clavulanic acid for pneumonia associated with influenza.

The WHO Department of Maternal, Newborn, Child and Adolescent Health reviewed its existing guidelines for treatment of CAP in children. This undertaking was informed by a systematic review of the current evidence of efficacy, safety and feasibility of antibiotic treatment options. Following expert consultation, the following recommendations were made with regard to antibiotic treatment of pneumonia in children:

- Fast breathing pneumonia: amoxicillin oral liquid or tablets, at least 40 mg/kg twice daily (80 mg/kg per day) x 5 days; in areas with low HIV prevalence, oral amoxicillin for 3 days.
- Severe pneumonia:
  - first-line: IM/IV ampicillin 50 mg/kg or benzylpenicillin injection 50 000 units/kg, every 6 hours for at least 5 days and IM/IV gentamicin, 7.5 mg/kg once a day for at least 5 days;
  - second-line: IV ceftriaxone.

For HIV-infected individuals, 10 days' therapy is recommended.

Rationale for antibiotic selection (from the application)

Proposed antibiotics for CAP were based on evidence from systematic reviews and are similar to recommendations in clinical practice guidelines – with the exception of azithromycin, which is not proposed for the EML because of safety concerns reported by the FDA (*2*). The applicants stated that, although no systematic review evidence was found for vancomycin, its inclusion for empirical therapy when MRSA is suspected, as suggested by the guidelines, was reasonable.

To minimize the occurrence of antibiotic resistance, and taking into consideration efficacy, safety, cost and availability, the application proposed the use of amoxicillin, amoxicillin + clavulanic acid, or phenoxymethylpenicillin as first-line empirical (core) therapy for mild to moderate CAP.

"Targeted" antibiotics were defined in the application as those necessary in cases of more severe illness, when alternatives to first-line options are required (e.g. penicillin allergy), and in specific situations where the likelihood of a particular organism warrants use.

Intravenous formulations such as benzylpenicillin, cefotaxime or ceftriaxone are proposed

for inclusion on the EML as targeted antibiotics for severe CAP. Doxycycline is targeted since it an alternative to first-line antibiotics.

In settings where melioidosis is endemic, ceftazidime can be used empirically as the third-generation cephalosporin of choice.

In keeping with a fluoroquinolone-sparing strategy, use of fluoroquinolones should be reserved for patients with allergies who cannot use beta-lactams and cephalosporins. Fluoroquinolones should be used with caution when tuberculosis is suspected as they could mask symptoms.

Use of clarithromycin should be restricted to severe pneumonia in adults and children aged over 5 years when atypical coverage is considered necessary.

Piperacillin + tazobactam should be restricted to severe pneumonia or patients at high risk for infection by resistant pathogens, e.g. by *Pseudomonas aeruginosa.*

In children, ampicillin and gentamicin could be used for severe pneumonia.

Vancomycin should be restricted to severe pneumonia when MRSA is suspected.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered.

The Expert Committee considered the antibiotics proposed in the application and selected first- and second-choice antibiotics for community-acquired pneumonia, in line with WHO guidelines, for inclusion on the EMLc.

The Committee considered the various antibiotics proposed in the application from the McMaster Group using the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion on the EML. Piperacillin + tazobactam, levofloxacin, vancomycin and ceftazidime were excluded.

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice	*Second choice*
Endorsement *Mild to moderate CAP*	amoxicillin phenoxymethylpenicillin	amoxicillin + clavulanic acid doxycycline
Severe CAP	ceftriaxone or cefotaxime in combination with clarithromycin	amoxicillin + clavulanic acid in combination with clarithromycin
Severe CAP children	amoxicillin + clavulanic acid ceftriaxone or cefotaxime gentamicin in combination with benzylpenicillin, ampicillin or amoxicillin	

Committee recommendations

The Expert Committee endorsed the inclusion of amoxicillin and phenoxymethylpenicillin as first-choice therapy options and of amoxicillin + clavulanic acid or doxycycline as second-choice therapy in mild to moderate CAP.

For severe CAP in adults, the Expert Committee endorsed the inclusion of ceftriaxone or cefotaxime in combination with clarithromycin (EML) as first-choice and amoxicillin + clavulanic acid in combination with clarithromycin as second-choice therapy. For severe CAP in children, the Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid; ceftriaxone or cefotaxime (EMLc); and gentamicin in combination with benzylpenicillin, ampicillin or amoxicillin (EMLc).

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Pharyngitis

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

More than 85% of pharyngitis is viral in origin. Pharyngitis is distinct from laryngitis, or inflammation of the larynx, for which there was no evidence for antibiotic effectiveness when objective outcomes were assessed (*1*). The major cause of bacterial pharyngitis is Group A *Streptococcus* (GAS). It is notable that penicillin resistance has yet to be demonstrated by these bacteria, although resistance to macrolides has increased. The major reason for treating GAS, other than symptomatic relief, has been to reduce complications such as rheumatic fever and post-streptococcal glomerulonephritis.

Summary of evidence (from the application)

A 2013 Cochrane review of antibiotic therapy for GAS pharyngitis in 17 randomized controlled trials (RCTs; 5352 participants) found no difference in symptom resolution between cephalosporins and penicillin (odds ratio (OR) 0.79; 95% confidence interval (CI) 0.55–1.12) but lower clinical relapse in adults given cephalosporins (OR 0.55; 95% CI 0.31–0.99) and no difference between macrolides and penicillin (OR 1.11; 95% CI 0.92–1.35) (*2*).

Duration of treatment has also been studied, with the premise that a shorter duration of antibiotic therapy, if effective, can reduce development of resistance, adverse events and cost. A 2012 Cochrane review summarized evidence for short-duration treatment (2–6 days) with newer agents (including azithromycin and clarithromycin) versus 10 days of penicillin (20 RCTs; 13 102 cases) in children with group A beta haemolytic streptococcus pharyngitis (*3*). The findings were in favour of shorter duration of treatment, with a reduction in the duration of fever (mean difference (MD) –0.30 days; 95% CI –0.45 to –0.14), throat soreness (MD –0.50 days; 95% CI –0.78 to –0.22), and lower risk of early clinical failure (OR 0.80; 95% CI 0.67–0.94). There were no differences in early bacteriological cure (OR 1.08; 95% CI 0.97–1.20) or late clinical recurrence (OR 0.95; 95% CI 0.83–1.08). However, there was a significantly greater risk of late bacteriological recurrence with the short-duration treatment (OR 1.31; 95% CI 1.16–1.48) (*3*).

Another Cochrane review (27 RCTs; 12 835 participants), which examined complications, reported that antibiotics reduced the risk of developing rheumatic fever (risk ratio (RR) 0.27; 95% CI 0.12–0.60) but there were too few events to comment on glomerulonephritis (*4*). In terms of suppurative complications, antibiotics reduced the incidence of acute otitis media (RR 0.30; 95% CI 0.15–0.58), acute sinusitis (RR 0.48; 95% CI 0.08–2.76), and peritonsillar abscess within two months (RR 0.15; 95% CI 0.05–0.47) compared with placebo.

The RCTs demonstrated the benefit of using antibiotics for GAS pharyngitis to reduce complications, which is of particular relevance in low- and middle-income countries. Although there is evidence that macrolides and cephalosporins may reduce duration of

symptoms, this must be weighed against the possibility for resistance to these agents, particularly since penicillin resistance in GAS has never been observed.

Guidelines (from the application)

The Infectious Diseases Society of America's *Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis* was rated as moderate to high quality in the application (5). It recommends penicillin or amoxicillin as the first-line agent for GAS pharyngitis. For individuals with serious penicillin allergy, macrolides (azithromycin or clarithromycin) are recommended.

Rationale for antibiotic selection (from the application)

Pharyngitis frequently has a viral cause. Thus, routine practice in some countries is not to treat pharyngitis at all; other countries typically use a delayed antibiotic prescription policy, and yet others heavily rely on microbiological testing to support an indication for antibiotic treatment.

In Group A streptococcal infections, antibiotics can reduce the incidence of rheumatic fever and suppurative complications. The fact that the evidence suggests similar overall outcomes with penicillin compared with other antibiotic classes, together with the importance of sparing macrolides and cephalosporins, argues strongly in favour of penicillin or amoxicillin as the first-line antibiotic. Clarithromycin can be used where there is a severe allergy to penicillin.

It should be noted that routine skin testing for allergy before first treatment with penicillins, which is current practice in some regions, is not necessary. For patients with known severe allergies who live in regions with high rates of macrolide resistance, cefalexin would be another option.

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

The Expert Committee noted that, since the vast majority of pharyngitis cases are caused by viruses, routine practice in some countries is not to treat the infection with antibiotics, others use a delayed antibiotic prescription policy, and others rely on diagnostic tests to support an indication for antibiotic treatment. Indeed, antibiotics have limited benefit in streptococcal pharyngitis, unless rheumatic fever is still a problem in a particular setting.

The Committee also noted the absence of indication for routine skin testing for allergy before first treatment with penicillins.

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The 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 on the EML and/or EMLc. The Committee endorsed the application's proposal.

Recommended first- and second-choice antibiotics are reported below. The first-

choice antibiotics are those that are generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	*Second choice*
Watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option		
Endorsement	phenoxymethylpenicillin	clarithromycin
	amoxicillin	cephalexin
Addition	N/A	clarithromycin (EMLc)
		(erythromycin as an alternative)

Committee recommendations

The Expert Committee noted that the appropriate first-line treatment option for pharyngitis is watchful waiting, symptom relief and no antibiotic treatment.

For suspected or proved bacterial pharyngitis, the Committee endorsed the use of phenoxymethylpenicillin or amoxicillin as first-choice therapy and clarithromycin (EML) or cefalexin (EML/EMLc) as second-choice therapy.

The Committee recommended the addition of clarithromycin to the EMLc (with erythromycin as an alternative) as second-choice therapy for suspected or proven bacterial pharyngitis in children.

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Sinusitis

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Sinusitis is generally diagnosed and treated in an ambulatory setting and most clinical trials have been conducted in this setting. Patients are typically treated on a clinical basis with no attempt made to obtain cultures for etiological determination. Given that more than 90% of cases of rhinosinusitis are due to viral infections, many of the trials have been conducted to test whether antibiotics offer any benefit compared with placebo.

Summary of evidence (from the application)

The question of whether sinusitis actually needs treatment with antibiotics has been addressed in several randomized controlled trials (RCTs). A 2012 Cochrane review (10 RCTs; 2450 participants) compared antibiotics with placebo for adults with rhinosinusitis and found that purulent secretions resolve faster with antibiotics (odds ratio (OR) 1.58; 95% confidence interval (CI) 1.13–2.22) (*1*). However, 27% of participants given antibiotics, versus 15% of those that received placebo, experienced adverse events (OR 2.10; 95% CI 1.60–2.77).

A 2013 Cochrane review of antibiotics for the common cold and purulent rhinitis (11 RCTs; 1047 participants) reported no difference in cure or persistent symptoms (risk ratio (RR) 0.95; 95% CI 0.59–1.51) (2). For adverse effects in the antibiotic group RR was 1.8 (95% CI 1.01–3.21) if antibiotics were initiated in patients with symptoms and signs of sinusitis lasting for 7 days or more. However, a more recent review of six RCTs showed a benefit of antibiotic treatment compared with placebo for symptomatic improvement after 3 days (OR 2.78; 95 %CI 1.39–5.58) and 7 days (OR 2.29; 95 % CI 1.19–4.41) after initiation in patients with symptoms and signs of sinusitis lasting for 7 days or more (*3*). After 10 days, however, improvement rates did not differ significantly between patients treated with antibiotics or given placebo (OR 1.36; 95 % CI 0.66–2.90).

In terms of selection of antibiotics, a 2014 Cochrane review (63 RCTs; 1915 participants) showed that amoxicillin or penicillin was superior to placebo in adults with maxillary sinusitis in terms of clinical failure (RR 0.66; 95% CI 0.47–0.94), but that the risk for clinical failure was higher with cephalosporins or macrolides compared with amoxicillin + clavulanic acid (RR 1.37; 95% CI 1.04–1.80) (*4*). However, cure or improvement was high in both groups (86% for placebo and 91% in antibiotic group). Adverse events were more common in antibiotic than in placebo groups (median 10.5% difference between groups, range 2–23%).

The RCTs demonstrate that antibiotics offer no benefit over placebo for sinusitis related to the common cold, which is most commonly caused by rhinovirus. Amoxicillin or penicillin may offer a moderate clinical benefit to patients with purulent sinusitis but this comes at increased risk of adverse events. Amoxicillin + clavulanic acid was shown to be superior to macrolides or cephalosporins.

Guidelines (from the application)

The Infectious Diseases Society of America (IDSA) guidelines recommend the use of amoxicillin + clavulanic acid as a first-line agent and a respiratory fluoroquinolone (levofloxacin or moxifloxacin) or doxycycline (for adult patients) in cases of allergy to beta-lactams (*5*). Amoxicillin + clavulanic acid, as opposed to amoxicillin alone, was recommended because of concern that there is growing prevalence of *Haemophilus influenzae* since the introduction of conjugate pneumococcal vaccines and an increasing prevalence of beta-lactamase production in these strains. However, there are few data to support the exact microbiology following introduction of the 13-valent conjugate pneumococcal vaccine. Other guidelines recommend amoxicillin with or without clavulanic acid and ceftriaxone for children who cannot be treated with oral antibiotics (*6, 7*).

In order to find a positive risk–benefit ratio for treatment decisions, guidelines recommend antibiotics only for patients with no spontaneous resolution within 10 days, severe symptoms, or worsening or double-sickening over 3–4 days.

Rationale for antibiotic selection (from the application)

Sinusitis frequently does not require antibiotics, particularly when it is associated with the common cold when antibiotics offer limited benefit. Delayed prescribing is another strategy for reducing the use of antibiotics. Evidence from systematic reviews suggests a higher risk of failure with cephalosporins or macrolides compared with amoxicillin + clavulanic acid.

Given the principle of using narrower-spectrum agents, amoxicillin alone may be effective; either amoxicillin or amoxicillin + clavulanic acid was therefore proposed as the core choice. Ceftriaxone can be used for severe sinusitis. Fluoroquinolones (levofloxacin, moxifloxacin) should be used only if beta-lactams cannot be used.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. 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 on the EML and/or EMLc. Ceftriaxone, levofloxacin and moxifloxacin were excluded.

Recommended first-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice	*Second choice*
Watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option		
Endorsement	amoxicillin	
	amoxicillin + clavulanic acid	

Committee recommendations

The Expert Committee noted that the appropriate first-line treatment option for sinusitis is watchful waiting, symptom relief and no antibiotic treatment.

The Committee endorsed the inclusion of amoxicillin and amoxicillin + clavulanic acid for suspected bacterial sinusitis as first-choice treatment on the EML and EMLc.

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Otitis media

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Acute otitis media is one of the most common infections in children. There has been controversy about the best approach, that is, whether otitis media should include early therapy or watchful waiting. On the one hand, avoidance of antibiotics could reduce resistance, adverse events and cost; on the other, concern has been raised about suppurative complications of otitis media if left untreated.

Summary of evidence (from the application)

A 2015 Cochrane review of 13 randomized controlled trials (RCTs; 3401 children) showed that antibiotics had not reduced pain at 24 hours after the start of treatment (risk ratio (RR) 0.89; 95% confidence interval (CI) 0.78–1.01) but almost a third fewer treated children had residual pain at 2–3 days (RR 0.70; 95% CI 0.57–0.86) (1). Immediate treatment with antibiotics was not associated with a reduction in the number of children with pain (RR 0.91, 95% CI 0.75 to 1.10) compared with expectant observation.

Antibiotics did reduce the number of children with tympanic membrane perforations (RR 0.37: 95% CI 0.18–0.76) but not abnormal tympanometry at 3 months (RR 0.97; 95% CI 0.76–1.24) or the number of children with late acute otitis media recurrences (RR 0.93; 95% CI 0.78–1.10). Adverse events such as vomiting, diarrhoea and rash occurred more often in children taking antibiotics than in placebo-treated children (RR 1.38; 95% CI 1.19–1.59).

A 2013 Cochrane review (5 RCTs, 1601 children) showed that one or two daily doses of amoxicillin, with or without clavulanic acid, were comparable to three or four doses for clinical cure at the end of therapy (RR 1.03; 95% CI 0.99–1.07), during therapy (RR 1.06; 95% CI 0.85–1.33) and at follow-up (RR 1.02: 95% CI 0.95–1.09) (*2*).

Guidelines (from the application)

Guidelines of the American Academy of Pediatrics and Family Physicians and of the Canadian Paediatric Society recommend treatment of acute otitis media in children with significant pain for longer than 48 hours and/or fever of 39 °C or higher (*3, 4*).

The Canadian Paediatric Society guidelines recommend amoxicillin as the antibiotic of choice when it is felt that acute otitis media should be treated with antibiotics (*3*). The American Academy of Pediatrics and Family Physicians recommend amoxicillin (but suggest amoxicillin + clavulanic acid if a child has already been exposed to amoxicillin in the previous 30 days) and cephalosporins for patients with allergy to penicillin (cefdinir, cefuroxime, cefpodoxime and ceftriaxone) (*4*).

Rationale for antibiotic selection (from the application)

Antibiotics may not be needed for otitis media and a strategy of watchful waiting may reduce unnecessary antibiotic use. Unless a child is under 2 years of age with bilateral otitis media (*4*), no antibiotics is a perfectly reasonable first-line option. Amoxicillin is the core antibiotic choice; amoxicillin + clavulanic acid is another option. Cefuroxime or ceftriaxone can be used for severe cases, minimizing exposure to third-generation cephalosporins.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. 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 on the EML and/or EMLc. Ceftriaxone and cefuroxime were excluded.

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice	*Second choice*
Watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option, unless a child is under 2 years of age with bilateral otitis media.		
Endorsement	amoxicillin	amoxicillin + clavulanic acid

Committee recommendations

The Expert Committee noted that the appropriate first-line treatment option for otitis media is watchful waiting, symptom relief and no antibiotic treatment, unless a child is under 2 years of age with bilateral otitis media.

The Committee endorsed the inclusion of amoxicillin as first-choice therapy and amoxicillin + clavulanic acid as second-choice therapy in suspected bacterial otitis media.

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Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Hospital-acquired pneumonia (HAP) is defined as pneumonia with onset starting more than 48 hours after admission to hospital. Patients are often exposed to different regimens of antibiotics and thus have an increased potential to acquire resistant bacteria, making antibiotic treatment more challenging.

Ventilator-associated pneumonia (VAP) is defined by the development of pneumonia while a patient is on a ventilator. Typically, the risk of infection with multidrug-resistant bacteria is high because of exposure to antimicrobials and the critical care setting. Various regimens have been assessed; a particular area of uncertainty is the need for double antipseudomonal coverage in severely ill patients.

The two syndromes were combined in the application because of the relative lack of data on HAP and because the guidelines consider these together.

Summary of evidence (from the application)

A 2015 Cochrane systematic review of 6 randomized controlled trials (RCTs; 1088 participants) comparing short-course with long-course antibiotics for HAP in critically ill patients, including patients with VAP (*1*). (There were few data from RCTs comparing duration of therapy in non-ventilated patients with HAP.) The authors found a short 7- or 8-day course of antibiotics, compared with a prolonged 10- to 15-day course, increased 28-day antibiotic-free days and reduced recurrence of VAP due to multi-resistant organisms (one study; n = 110; odds ratio (OR) 0.44; 95% confidence interval (CI) 0.21–0.95). For cases of VAP specifically due to non-fermenting Gram-negative bacilli, recurrence was greater after short-course therapy (two studies; *n* = 176; OR 2.18; 95% CI 1.14–4.16).

A 2013 review compared use of linezolid and vancomycin for HAP (9 RCTs; 4026 participants) (*2*). The authors found an adjusted absolute mortality risk difference (RD) between linezolid and vancomycin of 0.01% (95% CI –2.1% to 2.1%; *P* = 0.992) and an adjusted absolute clinical response difference of 0.9% (95% CI –1.2% to 3.1%; *P* = 0.409). However, there were more gastrointestinal side-effects with linezolid than with vancomycin (RD 0.01; 95% CI 0.00–0.02; *P* = 0.05).

In a 2013 systematic review (4 RCTs; 883 participants) comparing short-duration (7–8 days) and long-duration (10–15 days) antibiotic treatment of VAP there was no difference in mortality between the two groups (OR 1.20; 95% CI 0.84–1.72) (*3*). There was an increase in antibiotic-free days with the short-course treatment, with a mean difference of 3.40 days (95% CI 1.43–5.37), but no difference in relapses between the groups.

A 2008 systematic review (41 RCTs; 7015 patients) compared various antimicrobial

regimens for VAP and found no differences in mortality (*4*). The combination of ceftazidime and an aminoglycoside, however, was inferior to meropenem (risk ratio (RR) 0.70; 95% CI 0.53–0.93) for treatment failure. When monotherapy was compared with combined therapy, mortality rates were similar (RR 0.94; 95% CI 0.76–1.16) as were rates of treatment failure (RR 0.88; 95% CI 0.72–1.07).

Guidelines (from the application)

The application reviewed three guidelines – from the Infectious Diseases Society of America (IDSA), the National Institute for Health and Care Excellence (NICE) and the British Society for Antimicrobial Chemotherapy (BSAC) (*5*–*7*).

The NICE guidelines recommend that antibiotics for HAP be selected in accordance with local hospital policy (*5*). For early-onset infections (<5 days following admission to hospital) in patients with no recent exposure to antibiotics and no risk factors for multi-resistant pathogens, BSAC guidelines recommend the use of amoxicillin + clavulanic acid or of cefuroxime; for all other patients, cefotaxime or ceftriaxone, a fluoroquinolone, or piperacillin + tazobactam is recommended (*6*).

For HAP patients with suspected *Pseudomonas aeruginosa*, ceftazidime, ciprofloxacin, meropenem, or piperacillin + tazobactam could be used. The IDSA guidelines suggest the following for HAP: for low-risk patients (in terms of mortality and MRSA carriage) piperacillin + tazobactam, cefepime, levofloxacin or a carbapenem (*7*). Vancomycin or linezolid should be added for low-risk patients with a higher MRSA risk, and aztreonam and ceftazidime can be considered for Gram-negative coverage instead of the antibiotics listed above. For high-risk patients or patients who have received IV antibiotics during the previous 90 days, empirical double coverage for Gram-negatives is recommended, and aminoglycosides are listed as an option in addition to the antibiotics listed above. The recommended duration of treatment is 5–7 days for both HAP and VAP.

Rationale for antibiotic selection (from the application)

Amoxicillin + clavulanic acid is a core antibiotic that can be used within 5 days of hospital admission and if there is no prior antibiotic exposure or risk for resistance. Third-generation cephalosporins are another core choice, as is piperacillin + tazobactam.

The systematic reviews suggest non-inferiority between vancomycin and linezolid. Linezolid, however, was not proposed as a core antibiotic since it is proposed for the preservation list of those antibiotics that are last-line for highly resistant pathogens. Use of empirical vancomycin should be restricted to cases where MRSA is suspected.

Aminoglycosides are on the list for double antipseudomonal coverage if needed. The application proposed ceftazidime, cefepime and piperacillin + tazobactam for antipseudomonal coverage. It is recommended that the fluoroquinolones be used only when needed, for example, in the case of a serious allergy to first-choice antibiotics. Given the concern about carbapenem resistance, these agents should be used only when there are no other alternatives.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Committee decided not to include VAP in this review because of the need to have local microbiology and epidemiological data to guide the choice of antibiotics and because it is a relatively rare condition.

The Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first-choice antibiotics for HAP for inclusion on the EML and/or EMLc. As a result, levofloxacin, moxifloxacin, ciprofloxacin, ceftazidime, aztreonam, meropenem, imipenem, amikacin, gentamicin, tobramycin and vancomycin were excluded.

Recommended first-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended based on available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	*Second choice*
Endorsement	amoxicillin + clavulanic acid	
	cefotaxime	
	ceftriaxone	
Addition	piperacillin + tazobactam	

Committee recommendations

The Expert Committee reviewed the evidence and limited its recommendation to hospital-acquired pneumonia. It did not include antibiotics for ventilator-associated pneumonia in this section because the condition is relatively rare and the choice of empirical antibiotic treatment in national guidelines is based on local epidemiology/microbiology.

The Expert Committee endorsed the inclusion on the EML and EMLc of amoxicillin + clavulanic acid, cefotaxime and ceftriaxone for first-choice therapy in hospital-acquired pneumonia.

The Committee recommended the addition of piperacillin + tazobactam to the EML and EMLc for use in hospital-acquired pneumonia as one of the first-choice therapies.

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Sepsis in children

Applicant(s)

WHO Department of Maternal, Newborn, Child and Adolescent Health

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Sepsis is a major global cause of morbidity and mortality in children. It is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" (*1*). It can be caused by a wide variety of pathogens, although bacteria are responsible for most cases. The purpose of this review is to focus on empirical therapy for young children (age ≤5 years) presenting with sepsis or septic shock (where profound circulatory, cellular and metabolic abnormalities exist and contribute to a higher risk of mortality) (*1*).

Summary of evidence (from the application)

Of the two reviews considered in the application from the McMaster Group, one (two randomized controlled trials (RCTs); 127 participants) compared single and combination treatment regimens for suspected early neonatal sepsis. Results for mortality within 28 days were inconclusive (risk ratio (RR) 0.75; 95% confidence interval (CI) 0.19–2.9) because of the limited sample size (*2*). A review that compared beta-lactams with beta-lactams plus aminoglycosides for late-onset sepsis in neonates (one RCT; 24 participants) also found no significant difference in mortality (RR 0.17; 95% CI 0.01–0.2) but this trial was severely underpowered (*3*).

Guidelines (from the application)

The WHO Department of Maternal, Newborn, Child and Adolescent Health reviewed its existing guidelines for treatment of sepsis in children and neonates. This undertaking was informed by a systematic literature review of the current evidence of efficacy, safety and feasibility of antibiotic treatment options. Following expert consultation, the following recommendations were made for antibiotic treatment of sepsis in children and neonates:

- Serious bacterial infection, hospitalized infants with community-acquired infection: gentamicin injection and benzylpenicillin or ampicillin injection for 7–10 days.
- Serious bacterial infection, hospitalized infants, with risk of staphylococcal infection: cloxacillin injection and gentamicin injection for 10 days, continue with cloxacillin oral liquid or tablets for a total treatment duration of 21 days.
- Possible severe bacterial infection (PSBI) in young infants when referral is not possible, fast breathing as the only sign of illness: amoxicillin oral liquid or tablets for 7 days.
- PSBI in young infants when referral is not possible, clinical severe infection:

  Option 1: gentamicin IM injection once daily for 7 days and amoxicillin oral liquid or tablets twice daily for 7 days;

Option 2: gentamicin IM injection once daily for 2 days and amoxicillin oral liquid or tablets twice daily for 7 days.

- PSBI, young infants when referral is not possible, critically ill: ampicillin injection twice daily and gentamicin injection daily for 7 days.

For early-onset infection, National Institute for Health and Care Excellence (NICE) guidelines suggest use of IV benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless local bacterial resistance patterns suggest use of a different antibiotic (*4*). Although not formally a guideline, the American Academy of Pediatrics recommendation is for ampicillin and an aminoglycoside, typically gentamicin, for treatment of infants with suspected early-onset sepsis (*5*). If Gram-negative meningitis is suspected, cefotaxime should be used instead of an aminoglycoside. WHO's handbook of hospital care for children recommends ampicillin or penicillin and gentamicin as first-line antibiotic treatment for newborns with any signs of serious bacterial infection or sepsis (*6*). This handbook also specifies that use of cloxacillin and gentamicin should be considered if the clinical presentation suggests a higher risk of staphylococcal infection, such as extensive skin pustules, abscess or omphalitis in addition to signs of sepsis.

Rationale for antibiotic selection (from the application)

The evidence from systematic reviews is extremely limited and essentially makes no contribution to the decision on which antibiotics should be on the EMLc. The guidelines suggest a penicillin (ampicillin, penicillin or IV benzylpenicillin) together with gentamicin to cover Listeria and Gram-negative organisms; these antibiotics were proposed as core agents for neonatal sepsis.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the antibiotics proposed in the application from the WHO Department of Maternal, Newborn, Child and Adolescent Health, and selected first- and second-choice antibiotics for this indication, in line with the WHO guidelines, for inclusion on the EMLc.

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents. In particular, the Committee recommended the inclusion of cloxacillin and amikacin as potentially useful second-choice agents in infection suspected to be due to *Staphylococcus aureus* or gentamicin-resistant Gram-negative bacilli, respectively.

EML listings

Antibiotics proposed for both EML and EMLc unless specified
Endorsement indicates those antibiotics currently included on EML/EMLc
Addition indicates new antibiotics not currently on EML/EMLc

	First choice	*Second choice*
Endorsement	benzylpenicillin, ampicillin or amoxicillin	ceftriaxone or cefotaxime
	gentamicin	cloxacillin in combination with amikacin
Addition	N/A	amikacin

Committee recommendations

The Expert Committee endorsed the inclusion on the EMLc of gentamicin, in combination with benzylpenicillin or ampicillin or amoxicillin, as the first-choice treatment for sepsis in neonates and children, and of ceftriaxone or cefotaxime as a second-choice treatment.

The Committee recommended the addition of amikacin in combination with cloxacillin as a second-choice option for use in sepsis in neonates and children.

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Urinary tract infections

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Urinary tract infections (UTI) in the outpatient setting are a common reason for young women in particular to seek medical attention. Randomized controlled trials (RCTs) have addressed the type and duration of antibiotic treatments in this and other populations. Use of antibiotics for asymptomatic bacteriuria can drive antibiotic resistance and may also increase the risk for subsequent symptomatic UTI. While it is accepted practice that asymptomatic bacteriuria should be treated in pregnant women and in men about to undergo urological procedures, the benefits of therapy in other groups have been questioned and addressed in RCTs.

Summary of evidence (from the application)

A 2010 Cochrane systematic review (21 RCTs; 6016 participants) of acute uncomplicated UTI, found that sulfamethoxazole + trimethoprim (SMX–TMP) was equivalent to fluoroquinolones in achieving short-term (risk ratio (RR) 1.00; 95% confidence interval (CI) 0.97–1.03) and long-term (RR 0.99; 95% CI 0.94–1.05) symptomatic cure. Beta-lactam drugs were similar to SMX–TMP for short-term (RR 0.95, 95% CI 0.81 to 1.12) and long-term (RR 1.06, 95% CI 0.93 to 1.21) symptomatic cure but criteria for equivalence were not met (*1*). Short-term cure with nitrofurantoin was similar to that with SMX–TMP (RR 0.99; 95% CI 0.95–1.04) as was long-term symptomatic cure (RR 1.01; 95% CI 0.94–1.09).

For asymptomatic bacteriuria, a 2015 Cochrane review of nine RCTs (1614 participants) that compared antibiotics with placebo/no treatment showed that symptomatic UTI (RR 1.11; 95% CI 0.51–2.43), complications (RR 0.78; 95% CI 0. 35–1.74) and death (RR 0.99; 95% CI 0.70–1.41) were similar in the two treatment arms (*2*)

A 2014 Cochrane review of antibiotics for pyelonephritis in children (27 studies; 4452 children) reported no significant differences in duration of fever (2 studies; 808 children; mean difference (MD) 2.05 hours; 95% CI –0.84 to 4.94), persistent UTI at 72 hours after start of therapy (2 studies; 542 children; RR 1.10; 95% CI 0.07–17.41) or persistent kidney damage at 6–12 months (4 studies; 943 children; RR 0.82; 95% CI 0.59–1.12) between oral antibiotic therapy (10–14 days) and IV therapy (3 days) followed by oral therapy (10 days) (*3*). Similarly, there were no significant differences in persistent bacteriuria at the end of treatment (4 studies; 305 children; RR 0.78; 95% CI 0.24–2.55) or persistent kidney damage (4 studies; 726 children; RR 1.01; 95% CI 0.80–1.29) between IV therapy (3–4 days) followed by oral therapy and IV therapy (7–14 days) (*3*). No significant differences in efficacy were found between daily and three times daily administration of aminoglycosides (1 study; 179 children; persistent clinical symptoms at three days: RR 1.98; 95% CI 0.37–10.53).

Guidelines (from the application)

The Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend nitrofurantoin and SMX–TMP for acute uncomplicated cystitis in women (*4*). Amoxicillin + clavulanic acid is an alternative choice. Oral fosfomycin is recommended where available because of its minimal propensity for resistance. Ceftriaxone is recommended for acute pyelonephritis in women, as is ciprofloxacin. However, the guideline recommends that resistance rates for empirically selected antibiotics should be below 10% for pyelonephritis and below 20% for treatment of lower UTI, a threshold no longer met for fluoroquinolones in many countries. Amoxicillin + clavulanic acid and SMX–TMP are also recommended for empirical treatment in children aged 2–24 months by the American Academy of Pediatrics (*5*).

The European Association of Urology and European Society for Paediatric Urology state that antimicrobial choice is dictated by local resistance patterns (*6*). For young children, newborns and infants, parenteral therapy is advised, such as combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or a third-generation cephalosporin. For pyelonephritis during the first 6 months of life, ceftazidime plus ampicillin or an aminoglycoside plus ampicillin is recommended. A third-generation cephalosporin is recommended for children over 6 months of age for uncomplicated pyelonephritis while ceftazidime plus ampicillin or aminoglycoside plus ampicillin are suggested for complicated pyelonephritis. Although the guidelines list parenteral as well as oral cephalosporins, in addition to beta-lactams (including piperacillin, amoxicillin, amoxicillin + clavulanic acid, nitrofurantoin and aminoglycosides), fluoroquinolones are considered second- or third-line antibiotics for complicated urinary tract infection. The recommendations of the Italian Society for Pediatric Nephrology are similar (*7*).

Rationale for antibiotic selection (from the application)

The systematic review evidence showed that SMX–TMP was equivalent to fluoroquinolones for uncomplicated UTI and that nitrofurantoin was equivalent to SMX–TMP. SMX–TMP and nitrofurantoin are therefore proposed as core antibiotics. Fluoroquinolones were not included because of the need to preserve this class of antibiotics. Oral fosfomycin is proposed because of minimal resistance and good safety profile. Amoxicillin + clavulanic acid is proposed for young children while ampicillin and gentamicin are for children with severe illness. Fosfomycin is included as a core antibiotic.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. 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 on the EML and/or EMLc. Ampicillin, fosfomycin and gentamicin were excluded.

Amikacin was preferred to gentamicin because it is generally more active on Enterobacteriaceae; ciprofloxacin was added as a recommended first-line option for

empirical treatment in mild-to-moderate pyelonephritis and prostatitis because of its good bioavailability and penetration (if local/national epidemiological data allow).

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	*Second choice*
Endorsement		
Lower UTI:	amoxicillin amoxicillin + clavulanic acid sulfamethoxazole + trimethoprim nitrofurantoin	
Pyelonephritis and prostatitis: mild to moderate	ciprofloxacin	ceftriaxone or cefotaxime
Pyelonephritis and prostatitis: severe	ceftriaxone or cefotaxime	
Addition	amikacin (severe)	

Committee recommendations

The Expert Committee endorsed the inclusion of the following medicines as first-choice therapies on the EML and EMLc list:

- *lower UTI:* amoxicillin or amoxicillin + clavulanic acid or sulfamethoxazole + trimethoprim or nitrofurantoin
- *pyelonephritis or prostatitis, mild to moderate:* ciprofloxacin
- *pyelonephritis or prostatitis, severe:* ceftriaxone or cefotaxime.

The Expert Committee endorsed the inclusion of the following medicines as second-choice therapies on the EML and EMLc list:

- *pyelonephritis or prostatitis, mild to moderate:* ceftriaxone or cefotaxime.

The Committee recommended the addition of amikacin (in combination with ceftriaxone or cefotaxime) for severe pyelonephritis or prostatitis to the EML and EMLc for UTI therapy.

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Meningitis

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Acute bacterial meningitis is a medical emergency requiring prompt administration of antibiotics that penetrate well into inflamed meninges. Because of the severity of this infection, evidence from randomized controlled trials (RCTs) is limited; recommendations for antimicrobials are driven largely by susceptibility patterns of the most common pathogens together with experimental work in animal models.

Summary of evidence (from the application)

In a 2015 systematic review, chloramphenicol was compared with two penicillins, two cephalosporins and one tetracycline (5 RCTs; 1753 patients) (*1*). Chloramphenicol was associated with higher mortality than the other antibiotics (risk ratio (RR) 1.27; 95% confidence interval (CI) 1.00–1.60).

In contrast, a 2007 Cochrane review (19 RCTs; 1496 patients) that compared third-generation cephalosporins with treatment with penicillin or ampicillin-chloramphenicol found no differences in mortality (risk difference (RD) 0%; 95% CI 3% to 2%), risk of deafness (RD –4%; 95% CI –9% to 1%), or risk of treatment failure (RD –1%; 95% CI –4% to 2%) (*2*). There was a reduced risk of CSF culture positivity after 10–48 hours (RD –6%; 95% CI –11% to 0%) and an increased risk of diarrhoea (RD 8%; 95% CI 3% to 13%) for third-generation cephalosporins compared with penicillin/ampicillin-chloramphenicol (*2*).

A 2009 systematic review compared short-course (4–7 days) and long-course (7–14 days) antibiotics in children (5 RCTs; 426 patients) and found no difference in clinical success (odds ratio (OR) 1.24; 95% CI 0.73–2.11), long-term neurological complications (OR 0.60: 95% CI 0.29–1.27) or long-term hearing impairment (OR 0.59; 95% CI 0.28–1.23) (*3*).

Guidelines (from the application)

The National Institute for Health and Care Excellence (NICE) guidelines recommend ceftriaxone for patients aged 3 months and older, while younger infants should be treated with IV cefotaxime plus amoxicillin or ampicillin (*4*). It is also recommended that vancomycin be added for patients who have received prolonged or multiple exposures to antibiotics within the previous 3 months and for those who have recently travelled outside the United Kingdom.

IDSA (Infectious Diseases Society of America) guidelines recommend ampicillin and cefotaxime or an aminoglycoside for children less than 1 month of age, vancomycin and ceftriaxone or cefotaxime for children older than 23 months and adults up to 50 years of age, and addition of ampicillin for patients over 50 years for coverage of *Listeria monocytogenes* (*5*). Vancomycin plus cefepime, ceftazidime or meropenem is recommended for patients with penetrating trauma, who are post-neurosurgery or have a cerebrospinal shunt in

place.

Rationale for antibiotic selection (from the application)

Systematic review evidence suggests that chloramphenicol is associated with higher mortality than other antibiotics; it was therefore not proposed as a core antibiotic. Ampicillin, ceftriaxone and cefotaxime are proposed for multiple indications and are categorized as core, while aminoglycosides and vancomycin have more specific indications (e.g. by age or indication) and are therefore categorized as targeted, as are ceftazidime and meropenem.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The 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 on the EML and/or EMLc. Ceftazidime, amikacin, gentamicin and vancomycin were excluded, because the Committee considered that these antibiotics have limited or no indications in community-acquired acute bacterial meningitis.

The Committee recommended the inclusion of chloramphenicol as a second-choice option, particularly for epidemic bacterial meningitis.

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	*Second choice*
Endorsement	ceftriaxone or cefotaxime	ampicillin or amoxicillin chloramphenicol benzylpenicillin
Addition		meropenem (EMLc neonatal meningitis)

Committee recommendations

The Expert Committee endorsed the inclusion on the EML and EMLc of ceftriaxone or cefotaxime as first-choice option for use in suspected acute bacterial meningitis and of chloramphenicol, benzylpenicillin, ampicillin or amoxicillin as second-choice therapy, recognizing that the last three beta-lactams may be added as first-choice options in some countries for suspected acute bacterial meningitis in particular when *Listeria* is suspected.

The Committee recommended the addition of meropenem to the EMLc for use in neonates as a second-choice option to treat suspected acute bacterial meningitis where resistant Gram-negative organisms are the common causative agents.

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Complicated intra-abdominal infections

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Complicated intra-abdominal infections (cIAI) extend beyond the organ of origin into the peritoneal space and are associated with either peritonitis or abscess formation. They represent a diverse group of infections for which there are a broad spectrum of causative agents, although streptococci, Enterobacteriaceae and anaerobes predominate.

The application did not consider primary peritonitis from haematogenous dissemination (e.g. spontaneous bacterial peritonitis in the absence of an underlying infection of an organ), usually in the setting of an immunocompromised state, or dialysis-related infections.

Summary of evidence (from the application)

A 2005 review (*1*) evaluated 40 studies (5094 patients) to compare the efficacy of various antibiotics for secondary peritonitis (infection of the visceral organ that extends beyond the organ), such as complicated appendicitis or cholecystitis. Of the 40 studies, 38 compared two regimens of antibiotics and two compared three regimens. The antibiotics evaluated included carbapenems (meropenem or imipenem), as single agents compared with each other or with cephalosporin and metronidazole combination or with piperacillin + tazobactam; regimens of clindamycin and an aminoglycoside (gentamicin or amikacin or tobramycin) were compared with piperacillin + tazobactam. The trials were non-inferiority and all showed similar efficacy and no differences in mortality.

There were no differences in overall mortality or mortality due to infection when aminoglycoside and anaerobic regimens were compared with others, although confidence intervals were very large: odds ratio (OR) 2.03, 95% confidence interval (CI) 0.88–4.71 and OR 1.51, 95% CI 0.66–3.43, respectively. However, aminoglycoside-based regimens were shown to be inferior to all available comparators in terms of clinical success (OR 0.65; 95% CI 0.46–0.92). When broad-spectrum beta-lactams were compared with other regimens, there were no significant differences in infection-related mortality (OR 0.54; 95% CI 0.05–6.08) or in clinical cure (OR 1.22; 95% CI 0.56–2.66). When carbapenems were compared with other antibiotics, there was no significant difference in infection-related mortality (OR 0.78; 95% CI 0.30–2.03) or clinical cure (OR 0.71; 95% CI 0.47–1.07). For cephalosporins alone versus other agents, there was no difference in infection-related death (OR 0.63; 95% CI 0.10–3.84) or clinical success (OR 1.25; 95% CI 0.57–2.74). Similarly, for cephalosporin and anti-anaerobe regimens versus others, no difference was seen in infection-related death (OR 5.45; 95% CI 0.25–116.63) or clinical success (OR 0.71; 95% CI 0.29–1.75). However, the cephalosporins and beta-lactams were found to be superior in terms of clinical success to all other comparators (OR 3.21; 95% CI 1.49–6.92), as were fluoroquinolones combined with an anti-anaerobic agent (OR 1.74; 95% CI 1.11–2.73). As no specific antibiotic group was

compared with any other specific antibiotic group, no firm conclusions could be drawn from this evidence. It is possible that an outlier antibiotic group (e.g. aminoglycoside-based antibiotics) was driving the inferiority of the comparator group, while other groups within the comparator group could have been non-inferior or even superior to beta-lactams.

In a systematic review and meta-analysis comparing ertapenem with ceftriaxone (8 RCTs; 2883 patients), similar clinical success was reported (OR 1.13; 95% CI 0.75–1.71) (*2*). In a comparison of moxifloxacin with other antibiotics (4 RCTs; 2444 patients), results were similar for clinical cure (OR 0.80; 95% CI 0.61–1.04) and mortality (OR 0.91; 95% CI 0.45–1.83); there were more adverse events in the moxifloxacin group (OR 1.33; 95% CI 1.07–1.63), but the overall incidence of serious adverse events was similar (OR 1.23; 95% CI 0.59–2.60) (*3*).

A review comparing ertapenem with piperacillin + tazobactam (6 RCTs; 3161 patients) found no difference in clinical success (OR 1.15; 95% CI 0.89–1.49) (*4*). In an older systematic review (*5*), ciprofloxacin + metronidazole was found to be superior in terms of clinical cure to beta-lactam antibiotics (OR 1.69; 95% CI 1.20–2.30), however, the studies on which these observations were based were conducted before the recent increase in fluoroquinolone resistance.

Tigecycline, a tetracycline derivate and the first glycylcycline, received a boxed warning and the U.S. Food & Drug Administration (FDA) recommends against its use unless no better alternative agents are available. However, if the higher mortality were due to a lower efficacy of the drug, lower cure rates would be expected – which was not the case in the systematic review by Shen et al. 2015 (*6*), who found no difference in clinical and microbiological cure with tigecycline compared with imipenem or ceftriaxone in combination with metronidazole.

For most comparisons, the precision in the summary estimates is very wide, and none met the applicant's definition of non-inferiority; thus, a clinically significant difference cannot be ruled out. Moreover, the review of the clinical trial evidence does not point to superiority of any single agents or combination regimens. When statistically significant differences were found, these were obtained by aggregating several antibiotic groups at the expense of being able to identify the particular antibiotics responsible for better effects.

Guidelines (from the application)

The IDSA (Infectious Diseases Society of America) guideline (*7*) summarizes recommendations for empirical therapy. A very comprehensive approach is used, in terms of antibiotic choices, and the extensive list of recommended antibiotics includes several overlapping agents. This approach differs from the guiding principle of parsimony adopted for decisions on the EML.

For community-acquired infection in children, the recommendations are aminoglycoside-based regimens (ampicillin and gentamicin or tobramycin in combination with metronidazole or clindamycin), a carbapenem (ertapenem, meropenem, imipenem), a beta-lactam/beta-lactamase inhibitor combination (piperacillin + tazobactam, ticarcillin + clavulanic acid), or advanced-generation cephalosporins (cefotaxime, ceftriaxone,

ceftazidime, cefepime) in combination with metronidazole. With severe beta-lactam allergies, either an aminoglycoside or ciprofloxacin in combination with metronidazole is recommended.

Single-agent empirical therapy for adults with mild to moderately severe infections included cefoxitin, ertapenem, moxifloxacin, tigecycline and ticarcillin + clavulanic acid. For high-risk or severely ill adults, imipenem, meropenem, doripenem and piperacillin + tazobactam are recommended.

Recommended combination regimens include a cephalosporin (cefazolin, cefuroxime, ceftriaxone, cefotaxime) or a fluoroquinolone (ciprofloxacin or levofloxacin), each in combination with metronidazole, for mild to moderately severe infections. For high-risk community-acquired cases or severely ill patients, a carbapenem, piperacillin + tazobactam, a fluoroquinolone (ciprofloxacin or levofloxacin) or a cephalosporin (cefepime, ceftazidime), in combination with metronidazole, is recommended. The guidelines also make recommendations for empirical therapy for health care-associated cIAI. If extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are among the pathogens most commonly involved in this type of infection locally, regimens including a carbapenem and aminoglycosides – but not cephalosporins – are recommended. Ceftazidime is not recommended where >20% *Pseudomonas aeruginosa* are resistant. Vancomycin is recommended in addition to other antibiotics when coverage for MRSA is needed, based on the local antibiogram. Cefazolin, cefuroxime or ceftriaxone is recommended for empirical treatment of acute, mild to moderate, community-acquired cholecystitis. A carbapenem (imipenem, meropenem, doripenem), piperacillin + tazobactam, a fluoroquinolone (levofloxacin or ciprofloxacin), or cefepime, in combination with metronidazole, is recommended for severe community-acquired cholecystitis. For acute cholangitis following bilioenteric anastomosis, or for health care-associated biliary infection of any severity, any of the aforementioned antibiotics in combination with metronidazole could be used. The guidelines recommend against the use of ampicillin + sulbactam because of high resistance rates in *Escherichia coli*, against the use of cefotetan and clindamycin because of resistance in the *Bacteroides fragilis* group, and against aminoglycosides in non-severe, non-hospital-acquired cases; caution is recommended in the use of fluoroquinolones because of increasing resistance rates.

In contrast to the IDSA guidelines, the World Society of Emergency Surgery (WSES) guidelines (*8*) recommend either amoxicillin + clavulanic acid or ciprofloxacin in combination with metronidazole for extra-biliary or biliary acute intra-abdominal infection in patients who are not critically ill and have no risk factors for ESBLs. In those at increased risk for ESBLs and not critically ill, these guidelines recommend ertapenem or tigecycline for extra-biliary disease and tigecycline for intra-biliary disease. In critically ill patients with no risk for ESBLs, the guidelines recommend piperacillin-tazobactam for either extra- and intra-biliary disease. Where there is an increased risk of ESBLs, meropenem or imipenem with the option of adding fluconazole for extra-biliary disease and piperacillin and tigecycline with the option of fluconazole for intra-biliary disease are listed. For hospital-acquired intra-abdominal infection in the absence of critical illness where there is a risk for a multidrug-resistant organism, the guidelines recommend piperacillin, tigecycline and fluconazole. For hospital-acquired infection in a critically ill patient, piperacillin, tigecycline, and an

echinocandin (caspofungin, anidulafungin or micafungin) or a carbapenem (meropenem, imipenem, doripenem), teicoplanin, and an echinocandin (caspofungin, anidulafungin or micafungin) are recommended.

Rationale for antibiotic selection (from the application)

Since the overview of systematic reviews yielded inconclusive findings, the application's proposals for the EML are based on clinical practice guidelines (CPGs).

The proposed listings of antibiotics were based on the setting (community- versus hospital-acquired), as well as based on severity, applying the same approach as used in the IDSA guidelines.

For community-acquired non-severe infections, amoxicillin–clavulanic acid or a cephalosporin (cefotaxime or ceftriaxone) with metronidazole fulfil the curative intent as well as guarding against resistance. For hospital-acquired or severe cases, the same cephalosporins, with metronidazole, can be used, or piperacillin–tazobactam can be used instead of amoxicillin + clavulanic acid.

Fluoroquinolones should be considered as second-line therapy when beta-lactams/cephalosporins are contraindicated because of resistance concerns and there are concerns about potential harm. Of the fluoroquinolones, moxifloxacin has not been proposed, despite recommendations in one guideline, because of the availability of many other options and the possibility of higher adverse event rates. Vancomycin should be used for patients with suspected MRSA infection. Teicoplanin was not proposed due to redundancy and several indications for vancomycin across all syndromes. Ceftazidime, meropenem and the aminoglycosides are proposed as targeted antibiotics, based on local resistance data, as alternatives to the core antibiotics. For additional enterococcal coverage, ampicillin can be considered if the regimen being used would not cover enterococci (e.g. ceftriaxone/metronidazole).

Of the antibiotics listed in the guidelines, cefazolin, cefoxitin and cefuroxime were excluded for redundancy: ceftriaxone, which is listed, also offers broader Gram-negative coverage. Ticarcillin–clavulanate and piperacillin were also excluded: piperacillin–tazobactam is considered more appropriate and is listed for several syndromes. Tigecycline is a potential niche or last-resort antibiotic for multidrug-resistant pathogens or when no first- and second-line antibiotics can be used, but was not considered as a core or targeted antibiotic because of the boxed warning by the FDA relating to the presumed higher mortality rate. Cefepime was not proposed; it was felt to be redundant in view of the antibiotics already listed above, and there are concerns about inferiority in terms of mortality (see section on Febrile neutropenia). Ampicillin–sulbactam, cefotetan and clindamycin were not proposed: their use is discouraged in the IDSA guideline because of resistance concerns.

Ertapenem was proposed for the preserved list as it is considered a niche antibiotic, particularly for patients with suspected ESBL when *Pseudomonas aeruginosa* coverage is not needed. Of the available carbapenems, the application proposed listing only meropenem as it is the most frequently recommended carbapenem across all syndromes; imipenem and doripenem were therefore excluded.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The 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 on the EML and/or EMLc. Levofloxacin, ampicillin, ceftazidime, gentamicin, tobramycin and vancomycin were excluded.

Ceftazidime, gentamicin, tobramycin and vancomycin have limited indications in community-acquired cIAI. Ampicillin provides only enterococcal coverage, which is usually not needed for mild to moderate cIAI. Ciprofloxacin was preferred to levofloxacin (for parsimony, and to preserve levofloxacin as a treatment for multidrug-resistant tuberculosis).

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	*Second choice*
Endorsement		
Mild to moderate	amoxicillin + clavulanic acid	ciprofloxacin in combination with metronidazole
	ceftriaxone or cefotaxime in combination with metronidazole	
Severe	ceftriaxone or cefotaxime in combination with metronidazole	
Addition		
Severe	piperacillin + tazobactam	meropenem

Committee recommendations

The Expert Committee endorsed the inclusion of the following medicines on the EML and EMLc for complicated intra-abdominal infections (cIAI)

- mild to moderate: amoxicillin + clavulanic acid, or ceftriaxone or cefotaxime in combination with metronidazole as first-choice therapy, and ciprofloxacin in combination with metronidazole as second-choice therapy
- *severe:* ceftriaxone or cefotaxime in combination with metronidazole as first-choice therapy.

The Expert Committee recommended the addition of piperacillin + tazobactam as first-choice therapy and meropenem as second-choice therapy for severe complicated intra-abdominal infections.

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Skin and soft-tissue infections (including cellulitis and surgical site infections)

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Uncomplicated skin and soft-tissue infections refer to infections in which the host is healthy, including cellulitis, erysipelas, human and animal bites, and carbuncles. Complicated skin and soft-tissue infections occur when there may be vascular insufficiency, diabetes, pre-existing non-healing wounds. These infections are frequently polymicrobial and may be have a greater chance for being caused by organisms that are multi-resistant to antibiotics. Surgical site infections are included here as a subgroup of skin and soft-tissue infections.

Summary of evidence (from the application)

Twelve systematic reviews were found to be relevant (*1–12*). Many of the reviews were focused on comparisons of vancomycin with antibiotics such as linezolid and daptomycin, for infections that would be caused by MRSA.

In a 2014 systematic review and meta-analysis, six randomized controlled trials (RCTs; 1710 patients) compared daptomycin with other antibiotics (*1*). Clinical success was similar when daptomycin was compared with vancomycin (4 RCTs; odds ratio (OR) 1.19; 95% confidence interval (CI) 0.77–1.83) or with a penicillinase-resistant penicillin (2 RCTs; OR 1.05; 95% CI 0.84–1.31. Interpretation of this review was hampered by the fact that RCTs of both complicated and uncomplicated skin and soft-tissue infection were included. Similarly, another systematic review (3 RCTs; 1557 patients) that looked at clinical success found no superiority for daptomycin compared with semi-synthetic penicillins (OR 0.89; 95% CI 0.63–1.25) (*5*).

Several systematic reviews compared linezolid with vancomycin and other antibiotics (*2, 4, 6, 10–12*). One comparison that included 12 RCTs and 6093 patients showed linezolid to be superior in terms of clinical success (OR 1.67; 95% CI 1.31–2.12) (*6*). The authors concluded, however, that account should be taken of the use of less potent antistaphylococcal beta-lactams such as ceftriaxone in the comparator groups, the same all-cause mortality, and the higher probability of thrombocytopenia in the linezolid group, which may limit the use of linezolid to specific patient populations or to infections that are difficult to treat with other antibiotics.

A 2013 Cochrane review that compared linezolid with vancomycin for skin and soft-tissue infections (9 RCTs; 3144 patients) again found linezolid to be associated with a significantly better clinical (risk ratio (RR) 1.09; 95% CI 1.03–1.16) and microbiological cure rate in adults (RR 1.08; 95% CI 1.01–1.16) than vancomycin (*2*). There were fewer incidents of red man syndrome (RR 0.04; 95% CI 0.01–0.29), pruritus (RR 0.36, 95% CI 0.17–0.75) and rash (RR 0.27; 95% CI 0.12–0.58) with linezolid than with vancomycin, but more people in the linezolid group reported thrombocytopenia (RR 13.06; 95% CI 1.72–99.22), and nausea

(RR 2.45; 95% CI 1.52–3.94). Interpretation of these findings is complicated by a mix of complicated and uncomplicated infection and a high risk of bias reported by the authors.

Another systematic review that also compared linezolid with vancomycin for the treatment of Gram-positive infections, including skin and soft-tissue infections (9 RCTs; 2489 patients), found linezolid to have apparently higher efficacy than vancomycin (OR 1.40; 95% CI 1.01–1.95) (*10*).

For MRSA skin and soft-tissue infections, another systematic review (1 RCT; 59 patients) concluded that linezolid showed greater efficacy than vancomycin (RR 1.80; 95% CI 1.20–2.68) (*11*). A further review concluded that linezolid was superior to vancomycin for clinical and microbiological cure (OR 1.41; 95% CI 1.03–1.95 and OR 1.91; 95% CI 1.33–2.76, respectively) (*4*).

Finally, in a review that compared linezolid with vancomycin for MRSA skin and soft-tissue infections in hospital inpatients (4 RCTs; 174 patients), no significant difference in clinical cure was found between the treatment groups although the point estimate was in favour of linezolid (RR 2.94; 95% CI 0.35–25) (*12*).

For diabetic foot infections, a Cochrane systematic review (20 RCTs; 3791 patients) compared several antibiotic regimens including frequently-used antibiotics such as piperacillin + tazobactam, ampicillin + sulbactam, ceftazidime, vancomycin, ertapenem, imipenem, clindamycin and metronidazole (*3*). No antibiotic was found to be superior. However, the confidence intervals for most of the comparisons were very wide and so a potentially clinically significant difference could not be ruled out. The only comparisons that yielded significant differences were those of imipenem with piperacillin + tazobactam and piperacillin in combination with clindamycin: more adverse events were noted in the comparator groups (RR 3.5; 95% CI 1.56–7.86, and RR 3.70; 95% CI 1.19–11.11, respectively).

A systematic review comparing beta-lactam antibiotics with macrolides or lincosamides in patients with cellulitis or erysipelas (15 RCTs; 462 patients for clinical cure and 3032 for adverse events) reported similar clinical cure in all groups (RR 1.24; 95 % CI 0.72–2.41; P = 0.44); however, the small sample size limits inferences (*7*).

In a Cochrane review of interventions for non-surgically acquired cellulitis (25 RCTs; 2488 patients), macrolides and streptogramins were found to be more effective than penicillin (RR 0.84; 95% CI 0.73–0.98) (*8*). A Cochrane review of impetigo reported that, for oral therapy, penicillin was inferior to erythromycin (2 RCTs; 79 patients; RR 1.29; 95% CI 1.07–1.56) and to cloxacillin (2 RCTs; 166 participants; RR 1.15: 95% CI 1.01–1.32) for cure rates (*9*).

In summary, several systematic reviews reported higher cure rates with linezolid compared with vancomycin and beta-lactam antibiotics in the absence of an effect on mortality but at the cost of a significant risk of thrombocytopenia. No data suggest that daptomycin should be preferred over vancomycin. The findings on other comparisons were also inconclusive. Penicillin was inferior to erythromycin and cloxacillin for treatment of impetigo.

Guidelines (from the application)

The 2014 IDSA (Infectious Diseases Society of America) guidelines on skin and soft-tissue infections (*13*), which covers both paediatric and adult patients, recommend the following oral options for treatment of impetigo: dicloxacillin, cefalexin, erythromycin, clindamycin

and amoxicillin + clavulanic acid. For purulent skin and soft-tissue infections (most likely due to *Staphylococcus aureus*), recommendations include dicloxacillin, oxacillin, cefazolin, clindamycin, cefalexin, doxycycline and trimethoprim + sulfamethoxazole. For MRSA infections, or if MRSA is highly suspected, options include vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline and trimethoprim + sulfamethoxazole. For non-purulent skin and soft-tissue infections, penicillin G or V, clindamycin, nafcillin, cefazolin or cefalexin can be used, with the last two being specifically recommended for non-Type 1 penicillin allergy. For necrotizing infections of the skin, fascia and muscle, the IDSA guidelines recommend vancomycin or linezolid plus piperacillin + tazobactam or a carbapenem (meropenem, imipenem, ertapenem), or plus cefotaxime and metronidazole. Clindamycin in combination with penicillin is recommended for group A streptococcal necrotizing fasciitis.

Penicillin G, semisynthetic penicillins (nafcillin, oxacillin), cefazolin, vancomycin, clindamycin, doxycycline and ceftriaxone, as well as daptomycin, quinupristin + dalfopristin and linezolid, are listed as options for specific pathogens such as *Streptococcus*, *S. aureus, Clostridium sp., Aeromonas hydrophila* and *Vibrio* infections. For animal bites, amoxicillin + clavulanic acid is recommended as oral therapy. For IV therapy, ampicillin + sulbactam, piperacillin + tazobactam, second- and third-generation cephalosporins (cefuroxime, cefoxitin, ceftriaxone, cefotaxime) can be used. Other listed options include carbapenems, doxycycline, trimethoprim + sulfamethoxazole, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and, for anaerobic coverage, metronidazole and clindamycin. For human bites, amoxicillin + clavulanic acid and ampicillin + sulbactam should be used; carbapenems and doxycycline are also listed as alternatives. Vancomycin, daptomycin, linezolid and colistin can be used in the presence of selective multidrug-resistant bacteria.

For incisional surgical site infections of the intestinal or genitourinary tract, ticarcillin + clavulanic acid, piperacillin + tazobactam, carbapenems (imipenem, meropenem, ertapenem) are recommended single-drug regimens. Combinations regimens include ceftriaxone and metronidazole, a fluoroquinolone (ciprofloxacin or levofloxacin) and metronidazole, ampicillin + sulbactam plus gentamicin or tobramycin. After surgery of the trunk or extremity away from axilla or perineum, oxacillin or nafcillin, cefazolin, cefalexin, trimethoprim + sulfamethoxazole and vancomycin are suggested. For surgery of the axilla or perineum, either ceftriaxone or a fluoroquinolone (ciprofloxacin or levofloxacin) is recommended in combination with metronidazole. Other than the usual advice to avoid certain antibiotics (fluoroquinolones, doxycycline) in young children if at all possible, the recommendations were independent of the age of the patients.

For diabetic wounds, the 2012 IDSA guidelines recommend that clinically uninfected wounds are not treated with antibiotics; for infected wounds, antibiotic treatment should be supported by debridement as needed, as well as wound care (*14*). The following antibiotics are listed as potential options for mild infections: dicloxacillin, clindamycin, cefalexin, levofloxacin, amoxicillin + clavulanic acid; and doxycycline or trimethoprim + sulfamethoxazole for potential or confirmed MRSA infections. For moderate to severe infections, the list includes levofloxacin, cefoxitin, ceftriaxone, ampicillin + sulbactam, moxifloxacin, ertapenem, tigecycline, ciprofloxacin in combination with clindamycin, and

imipenem + cilastatin; and linezolid, daptomycin or vancomycin for (potential) MRSA. For (potential) *P. aeruginosa* infections, piperacillin + tazobactam is recommended; other options are ceftazidime, cefepime, aztreonam and carbapenems.

Rationale for antibiotic selection (from the application)

Amoxicillin + clavulanic acid, dicloxacillin, cefuroxime and cefalexin are recommended in the IDSA guidelines and all provide appropriate Gram-positive coverage for treatment for mild skin and soft-tissue infections and bites. For moderate to severe infections, IV antibiotics are proposed as core antibiotics and also provide appropriate Gram-positive and – if needed, depending on the choice within this group – Gram-negative and anaerobic coverage). If anaerobes are a consideration (e.g. abscesses), metronidazole, also proposed as a core antibiotic, can be combined with another antibiotic that lacks anaerobic coverage.

Clindamycin is proposed as a targeted antibiotic for mild infections, as an alternative agent if MRSA coverage is considered necessary, but as a core antibiotic for necrotizing fasciitis for moderate to severe infections. Other options if MRSA coverage is needed are doxycycline and sulfamethoxazole + trimethoprim, as well as vancomycin when IV treatment is needed; all are proposed as targeted antibiotics. Piperacillin + tazobactam is proposed as a targeted option in moderate to severe infections if broad Gram-negative coverage is needed (e.g. suspected polymicrobial necrotizing fasciitis, or diabetic foot infections that have already been extensively treated); meropenem is another alternative that provides even broader Gram-negative coverage.

Fluoroquinolones should be used only if no other option is available because of the potential for harm and resistance associated with this group of antibiotics; they are therefore proposed as targeted antibiotics.

Although data from RCTs have shown it to be superior to vancomycin and/or beta-lactams, linezolid was not included in the core or targeted antibiotic list because of several concerns. First, the beta-lactam comparators in many RCTs were not optimal antistaphylococcal beta-lactams (*6*). There was no significant effect on mortality, and the safety profile of linezolid is inferior because of the much higher risk of thrombocytopenia, which requires monitoring and has the potential to be a severe adverse event associated with prolonged hospitalization, platelet transfusion and admission to intensive care. Linezolid is therefore considered a niche antibiotic for patients in whom other options have failed or cannot be used; as such, it is proposed as a preserved list antibiotic. Despite being listed in clinical practice guidelines as potential options for treatment, daptomycin and quinupristin + dalfopristin were not proposed because of a lack of data showing any benefit over well-established treatment options. Daptomycin can be considered as an alternative for IV MRSA coverage if vancomycin cannot be used and has several other niche indications in other syndromes; it was proposed as a preserved list antibiotic.

Penicillin is not recommended for treatment of impetigo (based on guidelines and systematic review data). Nafcillin was not proposed: the IDSA guideline state that it is less convenient than cefazolin, and there is a risk of bone marrow suppression. Despite being listed in the IDSA guidelines, erythromycin is not included because of the concerns raised

in the guidelines about resistance in *S. aureus* and *S. pyogenes*. Colistin is proposed on the preserved list – it should only be used when no other options are available. Cefepime was not proposed: it was considered to be redundant in view of the antibiotics already listed, and there is concern about potential inferiority in terms of mortality (see section on Febrile neutropenia). Aminoglycosides, tigecycline, ceftaroline, aminoglycosides, ceftazidime and aztreonam are not considered for listing for skin and soft-tissue infections because of redundancy; other options are listed for several indications (e.g. vancomycin for MRSA, meropenem and piperacillin + tazobactam with broad spectrum activity against Gram-negatives including *P. aeruginosa*), however, cefepime, aztreonam and tigecycline are proposed on the preserved list for other syndromes.

The application did not propose ampicillin + sulbactam or ticarcillin + clavulanic acid due to redundancy because of the other beta-lactams proposed (amoxicillin + clavulanic acid and piperacillin + tazobactam). Ertapenem is proposed as a preserved antibiotic as a niche product for use if, for example, empirical ESBL coverage is needed, and imipenem + cilastatin was not considered due to redundancy because meropenem is proposed for many more syndromes. Both meropenem and piperacillin + tazobactam should be used only if there is a concern for infection by Gram-negatives resistant to other beta-lactams/ cephalosporins listed.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. 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 on the EML and/or EMLc.

For mild skin and soft-tissue infections, the following antibiotics were excluded: dicloxacillin (as cloxacillin was listed), cefuroxime, clindamycin, doxycycline, levofloxacin, ciprofloxacin, moxifloxacin and trimethoprim + sulfamethoxazole.

The antibiotics proposed in the application for severe skin and soft-tissue infections were excluded, since the Committee focused on the empirical treatment of common mild to moderate community-acquired infections.

The Committee listed amoxicillin + clavulanic acid and cloxacillin for reasons of parsimony, particularly because both antibiotics provide good coverage for staphylococcal (non-MRSA) and streptococcal infections, which are the leading causes of mild to moderate community-acquired skin and soft-tissue infections worldwide. Amoxicillin + clavulanic acid also provides good coverage for bites. The Committee listed cloxacillin, but noted that any IV antistaphylococcal penicillin is appropriate. For oral administration, cloxacillin, dicloxacillin and flucloxacillin are preferred because of their better bioavailability.

Recommended first- and second-choice antibiotics are reported below.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice	*Second choice*
Endorsement	amoxicillin + clavulanic acid cloxacillin	cefalexin

Committee recommendations

The Expert Committee endorsed the inclusion on the EML and EMLc of amoxicillin + clavulanic acid and cloxacillin (with a square box listing) as first-choice therapy and cefalexin as second-choice therapy for use in skin and soft-tissue infections.

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Acute infectious diarrhoea

Applicant(s)

WHO Department of Maternal, Newborn, Child and Adolescent Health

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Diarrhoea is an alteration in bowel movement characterized by an increase in the water content, volume and/or frequency of stools. Acute infectious diarrhoea can result from multiple causes depending on the setting and can include traveller's diarrhoea, for which therapy is typically empirical; it can also be cause-specific, e.g. cholera in epidemic settings. In this section, the focus is on empirical treatment in keeping with the other sections in which the major syndrome treated empirically is traveller's diarrhoea. However, because of the burden of infectious diarrhoea in low- and middle-income countries, the systematic review evidence for cause-specific diarrhoea is also assessed.

The potential benefits of antibiotics need to be weighed against increasing resistance rates, the risk of superinfection, and the harm caused by Shiga-toxin-producing organisms, which can be triggered by antibiotic exposure. Empirical treatment is usually considered in the case of febrile traveller's diarrhoea. In non-travel-related diarrhoea, empirical treatment should be considered only in the case of severe/invasive disease.

The following summary considers the review of acute infectious diarrhoea conducted by the McMaster group and the review of the cholera and dysentery (shigellosis) guidelines for paediatrics conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.

Summary of evidence (from the application)

A 2000 Cochrane review assessed the effect of oral antibiotics in traveller's diarrhoea (*1*). Twelve randomized controlled trials (RCTs) showed a greater cure by 72 hours for any antibiotics compared with placebo (odds ratio (OR) 5.90; 95% confidence interval (CI) 4.06–8.57). Patients who took antibiotics experienced more side-effects than those taking placebo (OR 2.37; 95% CI 1.50–3.75). Antibiotics reviewed included fluoroquinolones, + sulfamethoxazole + trimethoprim, ampicillin, azithromycin, aztreonam, bicozamycin, furazolidone, pivmecillinam, and trimethoprim alone. Although the authors had planned to compare the different antibiotics, this analysis was not carried out because of concerns about significant publication bias; it was therefore not possible to prioritize one antibiotic over the other.

A Cochrane review of patients with cholera (39 RCTs or quasi-experimental studies; 4623 participants) confirmed that antibiotics reduce both duration of diarrhoea and stool volume compared with placebo or no treatment; however, the list of antibiotics considered in the active treatment arm was so long (tetracycline, doxycycline, norfloxacin, sulfamethoxazole + trimethoprim, azithromycin, erythromycin, chloramphenicol, ciprofloxacin, furazolidone, pivmecillinam) that no conclusions could be reached on the

efficacy of specific drug classes (*2*). The authors provided head-to-head comparisons for duration of diarrhoea and clinical cure. Duration was more than a day less with a single dose of azithromycin than with ciprofloxacin (mean difference 32.4 hours; 95% CI 1.95–62.9) and clinical failure was less common (risk ratio (RR) 0.32; 95% CI 0.23–0.44). Similarly, tetracycline was found to be superior to sulfamethoxazole + trimethoprim (RR 0.56; 95% CI 0.34–0.92 for clinical failure).

Another Cochrane review assessed non-typhoidal *Salmonella* infection (12 RCTs; 767 participants) and concluded that there was a lack of benefit with antibiotic treatment; however, the review did not compare the various antibiotics (*3*). Microbiological cure was significantly better with fluoroquinolones compared with placebo (RR 0.33; 95% CI 0.20–0.56), but this did not translate into a benefit in clinically important outcomes. A further Cochrane review of RCTs treating *Shigella* dysentery concluded that there was insufficient evidence to consider any class of antibiotic to be superior (*4*). Fluoroquinolones were compared with beta-lactams in six RCTs with no significant difference; however, in trials where >90% of participants had confirmed *Shigella*, beta-lactams were more effective than fluoroquinolones (RR 4.68; 95% CI 1.74–12.59). Two trials compared fluoroquinolones with macrolides and two compared sulfamethoxazole + trimethoprim with beta-lactams; both comparisons showed no difference between groups. Single trials of sulfamethoxazole + trimethoprim versus furazolidone, oral gentamicin versus nalidixic acid, and sulfonamides versus tetracyclines showed no significant differences. The confidence intervals around the risk estimates were very wide, however, and a potentially patient-relevant difference between these antibiotics can therefore not be ruled out.

The evidence for both empirical therapy of traveller's diarrhoea and treatment of laboratory-confirmed diarrhoeal infection in low- and middle-income countries is extremely limited, and no data could be found favouring one antibiotic over another. Thus, recommendations are based on guidelines (see below). The exception is confirmed *Shigella* dysentery, for which beta-lactams appear to be superior to fluoroquinolones. For cholera, there is evidence that azithromycin is superior to fluoroquinolones. Sulfamethoxazole + trimethoprim should be avoided as it was found to be inferior to doxycycline.

Guidelines (from the application)

Although some guidelines give detailed recommendations for organism-specific infections, the McMaster application summarized therapy for empirical treatment.

The 2001 IDSA (Infectious Diseases Society of America) guidelines recommended fluoroquinolones for adults and sulfamethoxazole + trimethoprim for children with traveller's diarrhoea (*5*). A caveat is warranted, however, because of the increasing rates of fluoroquinolone-resistant *Campylobacter* infections. Moreover, patients with enterohaemorrhagic *Escherichia coli* infections should not be treated with antibiotics because of the higher risk of haemolytic uraemic syndrome. For cholera, these guidelines recommend doxycycline or tetracycline or a single dose of a fluoroquinolone. For non-typhi species of *Salmonella*, antibiotics are not routinely recommended, but if the infection is severe or if the patient is <6 months or >50 years old or has prostheses, valvular heart disease, severe atherosclerosis, malignancy or uraemia, sulfamethoxazole + trimethoprim (if susceptible), a fluoroquinolone or ceftriaxone is recommended. For *Shigella*, the choices

are sulfamethoxazole + trimethoprim, a fluoroquinolone, nalidixic acid, ceftriaxone and azithromycin.

The NICE (National Institute for Health and Care Excellence) guidelines for children <5 years recommend antibiotics in this age group only if there is suspected bacteraemia, extra-intestinal spread, age <6 months with *Salmonella*, malnourished or immunocompromised children, children with *C. difficile* enterocolitis, giardiasis, dysenteric shigellosis, dysenteric amoebiasis or cholera (*6*).

The American College of Gastroenterology guidelines recommend antibiotics – a fluoroquinolone, azithromycin or rifaximin – for traveller's diarrhoea only when the likelihood of bacterial pathogens is high enough to justify the potential adverse effects (*7*). For *C. difficile* infections, metronidazole and oral vancomycin are recommended (*8*).

The WHO Department of Maternal, Newborn, Child and Adolescent Health reviewed its existing guidelines for treatment of dysentery (shigellosis) and cholera in children. The reviews were informed by systematic literature reviews of the current evidence on the efficacy, safety and feasibility of antibiotic treatment options. Following expert consultation, the following recommendations were made for antibiotic treatment of dysentery and cholera:

Dysentery

- 1st line: ciprofloxacin oral liquid or tablets 15 mg/kg twice daily for 3 days
- 2nd line: IV/IM ceftriaxone injection 50–100 mg/kg for 2–5 days (to be used only when local strains of *Shigella* are known to be resistant to ciprofloxacin)
- Alternative 2nd line: azithromycin oral liquid or capsules 12 mg/kg on day 1 then 6 mg/kg on days 2–4 (total course: 4 days)

  or cefixime oral liquid or tablets, 8 mg/kg per day.

Cholera

Doxycycline oral liquid or tablets 4 mg/kg as a single dose *or* erythromycin oral liquid or tablets 12.5 mg/kg four times daily for 3 days *or* ciprofloxacin oral liquid or tablets 10–20 mg/kg twice daily for 5 days *or* azithromycin oral liquid or capsules 20 mg/kg as a single dose (only in epidemics).

In non-epidemic situations, antibiotics should be used only for children with severe dehydration.

Rationale for antibiotic selection (from the application)

For traveller's diarrhoea, sulfamethoxazole + trimethoprim was proposed as a core antibiotic for both children and adults, if treatment is deemed necessary. Azithromycin and fluoroquinolones, although listed as alternatives in the IDSA guidelines, should be used only if no other more appropriate options are available because of resistance concerns as well as the potential for harm. Given the superiority of beta-lactams for treatment of confirmed *Shigella* dysentery, ceftriaxone was proposed as a core antibiotic. For cholera, azithromycin should be considered first-line treatment on the basis of the systematic review evidence, with doxycycline as another option as listed in guidelines. Metronidazole (oral treatment preferred) and oral vancomycin are listed as core antibiotics for treatment

of *C. difficile* infections.

Ofloxacin, norfloxacin and nalidixic acid were not proposed because of redundancy; other fluoroquinolones were proposed for several more indications across all syndromes. Rifaximin was not included on the basis of redundancy; other options are available that are also relevant for other indications. Based on recommendations from experts from low- and middle-income countries on the advisory panel, chloramphenicol is proposed for the preserved list as a last-resort option for typhoid fever if no other antibiotics are available. Sulfamethoxazole + trimethoprim, ciprofloxacin and erythromycin are not recommended for treatment of cholera based on data from systematic reviews.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the various antibiotics proposed in the applications for alignment with WHO guidelines and under the guiding principle of parsimony and selected first- and second-choice antibiotics for acute infectious diarrhoea for inclusion on the EML and/or EMLc. As a result, levofloxacin and erythromycin were excluded. Ciprofloxacin was preferred to levofloxacin (for parsimony, and to preserve levofloxacin as a treatment for multidrug-resistant tuberculosis).

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	***Second choice***
In most non-bloody and non-febrile presentations, watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option.		
Endorsement		
Invasive bacterial diarrhoea/dysentery	ciprofloxacin	ceftriaxone cefixime azithromycin sulfamethoxazole + trimethoprim
Cholera	azithromycin (EMLc) doxycycline (EML	ciprofloxacin doxycycline (EMLc)
C. difficile	metronidazole	
Addition		vancomycin (oral) – *C. difficile*

Committee recommendations

The Expert Committee noted that, in most circumstances of non-bloody and non-febrile diarrhoea, watchful waiting, symptom relief and no antibiotic treatment is the appropriate first-line treatment option.

The Expert Committee endorsed the inclusion of the following medicines:

- Invasive bacterial diarrhoea/dysentery: ciprofloxacin as first-choice therapy and ceftriaxone or cefixime or azithromycin or sulfamethoxazole + trimethoprim as second-choice therapy (EML and EMLc)
- Cholera: azithromycin (EMLc) or doxycycline (EML) as first-choice therapy and ciprofloxacin or doxycycline (EMLc) as a second choice; doxycycline should be used only in severe/life-threatening cases
- *C. difficile* infection: metronidazole as first-choice therapy.

The Expert Committee recommended the addition of vancomycin (oral) as second-choice therapy for *C. difficile* infection.

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Sexually transmitted infections

Applicant(s)

WHO Department of Reproductive Health and Research

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Although there are a range of causative agents of urethritis, or inflammation of the urethra, the focus here is sexually transmitted infections (STIs). The McMaster application targeted comparative empirical therapy or comparative antimicrobials for *Gonococcus* and *Chlamydia trachomatis*, the two most common pathogens in infectious urethritis; syphilis was also included. The application from the WHO Department of Reproductive Health and Research was based on updated WHO treatment guidelines for gonorrhoea, syphilis and chlamydia.

STIs represent a major burden of disease worldwide and have significant negative effects on well-being. Gonorrhoea, syphilis and chlamydia often go undiagnosed and, if untreated, can result in serious complications such as pelvic inflammatory disease, infertility, ectopic pregnancy and miscarriage. Risk of infection with HIV is also increased in patients infected with gonorrhoea, syphilis or chlamydia.

Summary of evidence (from the application)

For treatment of urethritis due to *C. trachomatis*, one review of 23 randomized controlled trials (RCTs, 2384 participants) compared azithromycin with doxycycline and reported a non-significant summary estimate in favour of doxycycline (absolute risk benefit 1.5%; 95% confidence interval (CI) –0.1% to 3.1%) (*1*). An earlier review (12 RCTs; 1543 participants) also reported no difference between these two antibiotics for microbiological cure rates (risk difference 0.01; 95% CI –0.01 to -0.02%) (*2*).

However, another systematic review by the same first author found that clinical cure was significantly lower in studies since 2009 (67%) than in those before 2009 (85%), which raises the question of how useful azithromycin remains given the increase in observed resistance rates (*3*). The risk–benefit profile of doxycycline and the lower clinical cure rates in more recent studies with azithromycin support the use of doxycycline. This was confirmed by a recent non-inferiority trial, which reported that failure rates (0 in the doxycycline group, 5 in the azithromycin group) exceeded the margin for non-inferiority and concluded that non-inferiority was not established (*4*). Nevertheless, azithromycin still appears to be the best choice if adherence to a multi-day regimen is a concern.

A review of single-dose azithromycin versus erythromycin and amoxicillin for *C. trachomatis* infection during pregnancy (8 RCTs; 587 participants) found no difference in treatment success between the two groups (odds ratio (OR) 1.46; 95% CI 0.56–3.78) (*5*). Fewer adverse events were seen with azithromycin than with erythromycin (OR 0.11; 95% CI 0.07–0.18); erythromycin is thus not an ideal treatment for this indication given its poor risk–benefit profile.

Two systematic reviews comparing azithromycin with benzathine benzylpenicillin for syphilis were identified (*6, 7*). The newer review (3 RCTs) reported no difference (*6*) but confidence intervals exceeded those defined in the application for non-inferiority; the older, 2008, review (4 RCTs) showed better serological cure with benzathine benzylpenicillin (OR 1.75; 95% CI 1.03–2.97) (*7*).

The applicant considered that the evidence favours doxycycline over azithromycin for *C. trachomatis* urethritis and shows a questionable advantage of benzathine benzylpenicillin over azithromycin for the treatment of syphilis.

Guidelines (from the application)

Given the increase in fluoroquinolone resistance in gonococcal infections, the highest-ranked guidelines specific for urethritis, developed by the European Association of Urology, recommend ceftriaxone or cefixime, 800 mg, plus azithromycin for empirical treatment (*8*). They list azithromycin as the preferred antibiotic for *Chlamydia* and *Mycoplasma* infection and doxycycline as the preferred choice for *Ureaplasma urealyticum*.

The European guidelines on the management of non-gonococcal urethritis recommend doxycycline as the preferred antibiotic, and lymecycline, tetracycline or azithromycin as alternatives (*9*). Azithromycin is a second-line agent and is recommended for *Mycoplasma genitalium* infection; it should not be used routinely because of concern about macrolide resistance in *M. genitalium*. For persistent or recurrent non-gonococcal urethritis, if doxycycline was used as the first-line treatment, azithromycin and metronidazole can be used if *Trichomonas vaginalis* is prevalent in the local population. However, if azithromycin was used as first-line treatment, the recommended regimen is moxifloxacin and metronidazole.

United Kingdom guidelines for the management of non-gonococcal urethritis recommend doxycycline as the most effective treatment option, or a single dose of azithromycin with ofloxacin as an alternative (*10*). Guidelines from CDC (Centers for Disease Control and Prevention) include erythromycin, levofloxacin, or ofloxacin as alternatives to first-line regimens of azithromycin or doxycycline (*11*).

The 2016 guideline on syphilis published by WHO (*12*) recommends benzathine benzylpenicillin, or procaine benzylpenicillin as the next best alternative, for first-line treatment of both adults and children. Alternatives for patients who are allergic to penicillin include doxycycline. The use of ceftriaxone or azithromycin or erythromycin is discouraged unless there are no other options. Aqueous benzylpenicillin is recommended for congenital syphilis, with procaine benzylpenicillin as an alternative.

The United Kingdom guidelines from 2015 also recommend benzathine benzylpenicillin as first-line therapy, and azithromycin or doxycycline as a second-line alternative, with a caution about increasing resistance to macrolides (*13*). Other alternative regimens include ceftriaxone and amoxicillin, and erythromycin only if no other options are available. For neurosyphilis, procaine benzylpenicillin with concomitant probenecid is recommended as first choice. For congenital syphilis, again, aqueous benzylpenicillin and procaine benzylpenicillin are options.

Recommendations in the 2015 CDC guideline are essentially identical (*11*). However,

the CDC recommends aqueous crystalline benzylpenicillin as first-line treatment for neurosyphilis, rather than procaine benzylpenicillin and probenecid, which are recommended as an alternative.

Rationale for antibiotic selection (from the application)

Ceftriaxone IV or IM and oral cefixime were proposed as options for gonococcal urethritis. Doxycycline was proposed as the core antibiotic for the treatment of chlamydial/non-gonococcal urethritis, with or instead of azithromycin as suggested by most guidelines. Moreover, based on evidence from systematic reviews that the efficacy of azithromycin has been decreasing recently, and the boxed warning by the U.S. Food & Drug Administration on safety, azithromycin should be used only if doxycycline fails or is contraindicated or if there are major concerns about adherence to a multi-day doxycycline regimen. For syphilis, various forms of benzylpenicillin were proposed, depending on the disease form to be treated.

Of the antibiotics listed in the guidelines, fluoroquinolones – which are in most cases listed only as second- or third-line antibiotics – were not proposed for inclusion, given that several preferred options are already listed. Tetracycline and lymecycline were also not proposed because of redundancy with doxycycline, which is already listed for several other infectious syndromes. Erythromycin was not proposed because it gives rise to more frequent adverse events than azithromycin and because of the recommendation to avoid it as first- or second-line treatment for syphilis.

Other than congenital syphilis, these STIs are largely limited to the adult population; the systematic reviews and clinical practice guidelines identified therefore did not cover management in children, and no dosing recommendations for children were provided in the application.

WHO guidelines – Neisseria gonorrhoeae

The 2016 WHO guidelines for the treatment of *Neisseria gonorrhoeae* (*14*) make the following recommendations:

Genital and anorectal gonococcal infections

- Dual therapy:
  - ceftriaxone 250 mg IM as a single dose *plus* azithromycin 1 g orally as a single dose; OR
  - cefixime 400 mg orally as a single dose *plus* azithromycin 1 g orally as a single dose.
- Single therapy:
  - ceftriaxone 250 mg IM as a single dose
  - cefixime 400 mg orally as a single dose
  - spectinomycin 2 g IM as a single dose.

Oropharyngeal gonococcal infections

- Dual therapy:
  - ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g orally as a single dose;

OR

- cefixime 400 mg orally as a single dose plus azithromycin 1 g orally as a single dose.

- Single therapy:
  - ceftriaxone 250 mg IM as single dose.

Retreatment after treatment failure

- Dual therapy with one of the following combinations
  - ceftriaxone 500 mg IM as a single dose *plus* azithromycin 2 g orally as a single dose
  - cefixime 800 mg orally as a single dose *plus* azithromycin 2 g orally as a single dose
  - gentamicin 240 mg IM as a single dose *plus* azithromycin 2 g orally as a single dose
  - spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) *plus* azithromycin 2 g orally as a single dose.

Gonococcal ophthalmia neonatorum

- Treatment with one of the following options:
  - ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose
  - kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose
  - spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose.

Ocular prophylaxis of gonococcal ophthalmia neonatorum

- Treatment with one of the following options:
  - tetracycline hydrochloride 1% eye ointment
  - erythromycin 0.5% eye ointment
  - povidone iodine 2.5% solution (water-based)
  - silver nitrate 1% solution
  - chloramphenicol 1% eye ointment.

WHO guidelines – Treponema pallidum and congenital syphilis

The 2016 WHO guidelines for the treatment of *Treponema pallidum* (syphilis) (*12*) make the following recommendations:

Early syphilis (primary, secondary and early latent syphilis of not more than 2 years' duration) – adults and adolescents

- Treatment with one of the following options:
  - benzathine benzylpenicillin 2.4 million units once IM, over no treatment
  - benzathine benzylpenicillin 2.4 million units once IM, over procaine benzylpenicillin 1.2 million units daily IM for 10–14 days.
- When benzathine or procaine penicillin cannot be used:
  - doxycycline 100 mg twice daily orally for 14 days; OR
  - ceftriaxone 1 g IM once daily for 10–14 days; OR
  - azithromycin 2 g once orally (special circumstances).

Early syphilis (primary, secondary and early latent syphilis of not more than 2 years' duration) – pregnant women

- Treatment with one of the following options:
  - benzathine benzylpenicillin 2.4 million units once IM, over no treatment
  - benzathine benzylpenicillin 2.4 million units once IM, over procaine benzylpenicillin 1.2 million units IM once daily for 10 days.
- With caution, when benzathine or procaine benzylpenicillin cannot be used:
  - erythromycin 500 mg orally four times daily for 14 days; OR
  - ceftriaxone 1 g IM once daily for 10–14 days; OR
  - azithromycin 2 g once orally.

Late syphilis (infection of more than 2 years' duration without evidence of treponemal infection – adults and adolescents

- Treatment with one of the following options:
  - benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over no treatment.
  - benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over procaine benzylpenicillin 1.2 million units IM once daily for 20 days.
- When benzathine or procaine penicillin cannot be used:
  - doxycycline 100 mg twice daily orally for 30 days.

Late syphilis (infection of more than 2 years' duration without evidence of treponemal infection – pregnant women

- Treatment with one of the following options:
  - benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over no treatment
  - benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over procaine benzylpenicillin 1.2 million units IM once daily for 20 days.
- With caution, when benzathine or procaine benzylpenicillin cannot be used:
  - erythromycin 500 mg orally four times daily for 30 days.

Congenital syphilis in infants

- Treatment with one of the following options:
  - benzylpenicillin 100 000–150 000 U/kg IV daily for 10–15 days
  - procaine benzylpenicillin 50 000 U/kg single dose IM daily for 10–15 days.

WHO guidelines – *Chlamydia trachomatis*

The 2016 WHO guidelines for the treatment of Chlamydia trachomatis (15) make the following recommendations:

Uncomplicated genital chlamydia

- Treatment with one of the following options:

  - azithromycin 1 g orally as a single dose
  - doxycycline 100 mg orally twice a day for 7 days.
- OR one of the following alternatives:
  - tetracycline 500 mg orally four times a day for 7 days
  - erythromycin 500 mg orally twice a day for 7 days
  - ofloxacin 200–400 mg orally twice a day for 7 days.

Anorectal chlamydial infection

- In order of preference:
  - doxycycline 100 mg orally twice a day for 7 days
  - azithromycin 1 g orally as a single dose.

Genital chlamydial infection in pregnant women

- In order of preference:
  - azithromycin 1 g orally as a single dose
  - amoxicillin 500 mg orally three times a day for 7 days
  - erythromycin 500 mg orally twice a day for 7 days.

Lymphogranuloma venereum

- In order of preference:
  - doxycycline 100 mg orally twice daily for 21 days
  - azithromycin 1 g orally, weekly for 3 weeks.

Chlamydial ophthalmia neonatorum

- In order of preference:
  - azithromycin 20 mg/kg per day orally, one dose daily for 3 days
  - erythromycin 50 mg/kg per day orally, in four divided doses daily for 14 days.

Ocular prophylaxis of chlamydial ophthalmia neonatorum

- Treatment with one of the following options:
  - tetracycline hydrochloride 1% eye ointment
  - erythromycin 0.5% eye ointment
  - povidone iodine 2.5% solution
  - silver nitrate 1% solution
  - chloramphenicol 1% eye ointment.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Committee considered the various antibiotics proposed in the applications, aligning recommendations to WHO STI guidelines for combination therapy (gonorrhoea) and including additional second-choice medicines (gentamicin and spectinomycin).

Recommended first- and second-choice antibiotics are reported below.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	*Second choice*
Endorsement		
Neisseria gonorrhoeae	ceftriaxone in combination with azithromycin (EML)	cefixime (in combination with azithromycin) (EML) Gentamicin (EML) Spectinomycin (EML)
Chlamydia trachomatis	azithromycin (EML) doxycycline (EML)	
Trichomonas vaginalis	Metronidazole (EML)	
Syphilis	benzathine benzylpenicillin (EML) procaine benzylpenicillin (EMLc) benzylpenicillin	procaine benzylpenicillin (EML)
Addition	erythromycin 0.5% eye ointment (EMLc for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*)	

Committee recommendations

The Expert Committee endorsed the inclusion of the following medicines for use in sexually transmitted infections:

- *Neisseria gonorrhoeae:* first-choice therapy is ceftriaxone in combination with azithromycin and second-choice therapy is cefixime in combination with azithromycin, or gentamicin or spectinomycin.
- *Chlamydia trachomatis:* first-choice therapy is azithromycin or doxycycline.
- *Trichomonas vaginalis:* first-choice therapy is metronidazole.
- Syphilis: first-choice therapy is benzathine benzylpenicillin or procaine benzylpenicillin (EMLc) or benzylpenicillin, and second-choice therapy is procaine benzylpenicillin (EML).

The Expert Committee recommended the addition of erythromycin eye ointment to Section 21.1 of the EMLc for use in *Chlamydia trachomatis* and *Neisseria gonorrhoeae* as first-choice therapy in neonates for both infections.

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Exacerbations of chronic obstructive pulmonary disease

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Exacerbations of chronic obstructive pulmonary disease (COPD) are an important health-care burden. Although treatment can involve bronchodilators and anti-inflammatory agents, including steroids, antimicrobials are frequently used on the basis that a bacterial infection is suspected of acting as a trigger to the episode. However, antibiotics are indicated in only a minority of patients presenting with exacerbated COPD (see guidelines summaries below).

Summary of evidence (from the application)

The highest-quality review was a 2012 Cochrane review (16 randomized controlled trials (RCTs); 2068 participants) (*1*). There was no significant benefit in using antibiotics compared with not using antibiotics in outpatients when treatment was restricted to available antibiotics (risk ratio (RR) 0.80; 95% confidence interval (CI) 0.63–1.01) but there was evidence of benefit for inpatients (RR 0.77; 95% CI 0.65–0.91). In contrast, an older and lower-quality systematic review (9 RCTs; 1101 patients) found a small clinical benefit with antibiotic treatment but provided no further details of the population who benefited (*2*). Similarly, a systematic review from 2008 (10 RCTs; 959 participants) found higher treatment failure rates with placebo than with antibiotic treatment overall (RR 0.54; 95% CI 0.32–0.92) and in hospitalized patients (RR 0.34; 95% CI 0.20–0.56) but not ambulatory patients (RR 0.88; 95% CI 0.56–1.39) (*3*). In-hospital mortality was also found to be lower with antibiotic treatment (RR 0.22; 95% CI 0.08–0.62). These reviews did not compare antibiotics.

Of two reviews that compared different antibiotic agents, one compared first- and second-line antibiotics (12 RCTs; 2261 participants) and reported that first-line antibiotics (amoxicillin, ampicillin, pivampicillin, sulfamethoxazole + trimethoprim, and doxycycline) were associated with lower treatment success than second-line agents (amoxicillin + clavulanic acid, macrolides, second- or third-generation cephalosporins, and quinolones) (odds ratio (OR) 0.51; 95% CI 0.34–0.75 (*4*). Interpretation of these findings was difficult, however, since specific classes of antibiotics were not compared separately, i.e. no head-to-head comparisons were provided, and many of the antibiotics considered second-line in this review are nowadays considered to be first-line agents. The second review (5 RCTs; 287 participants), found no differences in treatment success, adverse events or mortality between patients treated with penicillins and those treated with sulfamethoxazole + trimethoprim but did not meet the applicant's criteria for non-inferiority (*5*).

In terms of duration of treatment, one systematic review (21 RCTs; 10 698 participants) compared the outcome for short-duration treatment (up to 5 days) with longer durations (*6*). With reasonably small confidence intervals, the authors found no difference in efficacy

(RR 0.99; 95% CI 0.90–1.08 for clinical cure at the 4-week mark). This was confirmed by another systematic review from the same year, which included fewer studies (*7*).

In summary, the evidence from RCTs was insufficient for the applicants to recommend one antibiotic or class of antibiotics over another; guidelines therefore informed the choices of antibiotics for the EML. Limiting the duration of treatment to 5 days was supported by appreciable evidence.

Guidelines (from the application)

The 2004 American Thoracic Society (ATS) and European COPD guidelines recommend that antibiotics for outpatient treatment may be initiated if there are altered sputum characteristics (*8*). Amoxicillin/ampicillin, doxycycline, azithromycin, clarithromycin, dirithromycin, roxithromycin, levofloxacin and moxifloxacin were potential candidates, depending on local bacterial resistance patterns. For hospitalized patients, amoxicillin + clavulanic acid, respiratory fluoroquinolones (levofloxacin and moxifloxacin), and combination therapy were recommended if *Pseudomonas* and other Gram-negatives were suspected.

National Institute for Health and Care Excellence (NICE) guidelines recommend antibiotics only if there is purulent sputum or clinical or radiographic evidence of pneumonia in which case an aminopenicillin, a macrolide or a tetracycline could be used, taking into account local resistant patterns (*9*).

Canadian guidelines distinguish acute tracheobronchitis, which does not need antibiotic treatment, from chronic bronchitis with and without risk factors (complicated), and chronic suppurative bronchitis (*10*). For chronic bronchitis without risk factors, macrolides, second- and third generation cephalosporins, amoxicillin, doxycycline, and sulfamethoxazole + trimethoprim are recommended. In complicated bronchitis (with risk factors), fluoroquinolones and beta-lactams/beta lactamase inhibitors are recommended. In chronic suppurative bronchitis, targeted treatment of the identified pathogen is recommended.

The U.S. Food & Drug Administration (FDA) published a boxed warning against the use of fluoroquinolones for this indication because of side-effects associated with antibiotics of this class (*11*). The main concerns related to disabling and potentially permanent adverse effects on tendons, muscles and joints, and to peripheral neuropathy and central nervous system effects, also reported in otherwise healthy patients. The FDA continues to recommend the use of fluoroquinolones in life-threatening infections where the potential benefit outweighs the risk.

Rationale for antibiotic selection (from the application)

Based on the guidelines, amoxicillin – alone or in combination with clavulanic acid – and a cephalosporin (cefuroxime or cefalexin) were proposed as core antibiotics providing appropriate coverage. Clarithromycin and doxycycline are alternatives if beta-lactams or cephalosporins cannot be used. Azithromycin was not proposed as an alternative to clarithromycin because of safety concerns. Dirithromycin and roxithromycin were not proposed as they offer no benefit compared with clarithromycin, which is also

recommended for other syndromes. Sulfamethoxazole + trimethoprim was not proposed as it was listed in only one of the guidelines and is not frequently used for this indication. Because of the side-effect profile of fluoroquinolones and the emergence of resistance, levofloxacin should be used only if no better options among the antibiotics listed here are available. Moxifloxacin was not proposed as it is not considered to be superior to levofloxacin, and levofloxacin is listed for several other indications.

COPD is a disease of the adult patient population and it was therefore not surprising that no systematic review data or guidelines were found for management in the paediatric population. No treatment recommendations were made for paediatric patients.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. 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 on the EML. As a result, cefuroxime, clarithromycin and levofloxacin were excluded since other narrower-spectrum options were available.

Recommended first- and second-choice antibiotics are reported below. First-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice – EML	***Second choice – EML***
Antibiotics are not needed in all patients presenting with exacerbations of COPD		
Endorsement	amoxicillin	cefalexin
	amoxicillin + clavulanic acid	doxycycline

Committee recommendations

The Expert Committee noted that antibiotics are not required in all patients presenting with COPD exacerbations.

The Committee endorsed the inclusion on the EML of amoxicillin and amoxicillin + clavulanic acid as first-choice therapy and of cefalexin and doxycycline as second-choice therapy for use in suspected bacterial exacerbations of COPD.

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Bone and joint infections

Applicant(s)

McMaster Group

Introduction

(description of the condition/infecting organisms/public health need)

Bone and joint infections include infections of the native bone or joint, i.e. osteomyelitis and septic arthritis, as well as prosthetic joint infections (which are increasing in incidence as a result of the ever-greater number of joint replacements). Treatment is rarely empirical and targeted treatment based on microbiology is emphasized for this type of infection.

Summary of evidence (from the application)

One Cochrane review compared antibiotics for treating chronic osteomyelitis in adults (*1*). There were only eight small randomized controlled trials (RCTs) with a total of 282 participants; these provided very limited information because a lack of power meant that no significant differences could be found between various combinations of oral and parenteral agents, and none of the comparisons met the definition of non-inferiority.

Another review compared fluoroquinolones (ciprofloxacin, ofloxacin and pefloxacin) with various beta-lactams (imipenem + cilastatin, ampicillin + sulbactam, amoxicillin + clavulanic acid, cefazoline or ceftazidime, broad-spectrum cephalosporins or nafcillin in combination with an aminoglycoside) for osteomyelitis (7 RCTs; 411 participants) (*2*). There was no difference in treatment success between fluoroquinolones and beta-lactams (194 patients; odds ratio (OR) 0.99; 95% confidence interval (CI) 0.51–1.91); confidence intervals were wide and non-inferiority criteria were not met.

Given the small size of the studies and the resultant wide confidence intervals, no conclusions could be drawn from the systematic reviews, and recommendations from clinical practice guidelines were needed to inform the selection of antibiotics proposed for the EML.

Guidelines (from the application)

Clinical practice guidelines from the Infectious Diseases Society of America (IDSA) provide recommendations for treatment of prosthetic joint infection (*3*). Where the prosthetic joint is retained after debridement, they recommend rifampicin in combination with pathogen-specific therapy: nafcillin, cefazolin or ceftriaxone for methicillin-susceptible staphylococci; vancomycin for methicillin-resistant staphylococci; penicillin or ampicillin for penicillin-susceptible *Enterococcus* spp; vancomycin for penicillin-resistant *Enterococcus* spp; cefepime or meropenem for *Pseudomonas aeruginosa*; cefepime or ertapenem for *Enterobacter* spp; an intravenous beta-lactam based on susceptibility or ciprofloxacin for Enterobacteriaceae; penicillin or ceftriaxone for beta-haemolytic streptococci, and penicillin or ceftriaxone for *Propionibacterium acnes*. An oral antibiotic, such as a fluoroquinolone (ciprofloxacin or levofloxacin), or sulfamethoxazole + trimethoprim, minocycline, doxycycline, or first-generation cephalosporin (e.g. cefalexin) or antistaphylococcal penicillins along with rifampicin

is recommended for methicillin-susceptible *S. aureus* infections. Cephalexin, dicloxacillin, sulfamethoxazole + trimethoprim, and minocycline are recommended choices for chronic suppressive therapy (if required) following an initial treatment course. When the treatment is a 1-stage approach, a similar approach, i.e. pathogen-specific therapy with rifampicin followed by longer-term rifampicin plus a companion oral antibiotic, is recommended for patients with *S. aureus* infections. The IDSA guidelines for vertebral osteomyelitis suggest a combination of vancomycin and a third- or fourth-generation cephalosporin for empirical use if required, but the general approach is to identify and then target the pathogen (*4*). First-line antibiotics for vertebral osteomyelitis pathogens are the same as those for prosthetic joint infections, with the addition of ciprofloxacin for *Salmonella* spp.

Rationale for antibiotic selection (from the application)

Based on the epidemiology of pathogens typically encountered in this type of infection, the application proposed the most appropriate antibiotics for possible empirical and targeted treatment. Empirical treatment should be avoided unless patients need immediate antibiotic treatment or if it is impossible to obtain a sample for microbiological examination. Choice of antibiotic for empirical treatment should be based on the pathogens deemed most likely to be involved. As treatment depends heavily on the identified pathogen, no distinction was made between core and targeted antibiotics: all antibiotics were proposed in a single group (i.e. core) for this indication.

Of the antibiotics proposed in the guidelines, cefepime was not proposed for inclusion on the EML because of safety concerns (see summary for Febrile neutropenia) in settings where an alternative agent (meropenem) is available. However, cefepime is considered a niche antibiotic for treatment of otherwise beta-lactam-resistant pathogens, as a carbapenem-sparing agent. Ertapenem, in keeping with other syndromes, was also proposed as a niche antibiotic when broad Gram-negative coverage without coverage of *P. aeruginosa* is needed. Minocycline was not proposed because doxycycline was proposed for this and several other syndromes. Dicloxacillin, rather than nafcillin, is proposed as an antistaphylococcal penicillin because it is also proposed for several other syndromes. Finally, rifampicin was listed as a niche antibiotic specifically for treatment of rifampicin-susceptible staphylococci in the presence of a prosthetic joint.

No data or guidelines specifically for children were identified and no recommendation for dosage in children was proposed.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. 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 on the EML and/or EMLc. The following antibiotics were excluded:

- ampicillin, benzylpenicillin, levofloxacin, ciprofloxacin, sulfamethoxazole + trimethoprim, and doxycycline, since these antibiotics are used mostly for targeted therapy;

- cephalexin because of redundancy;
- vancomycin because MRSA is a frequent cause of community-acquired infections only in a minority of countries.

The Committee recommended inclusion of cloxacillin (with a square box), and considered that any IV antistaphylococcal penicillin would be appropriate. For oral administration, cloxacillin, dicloxacillin and flucloxacillin are preferred because of their better bioavailability.

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice	*Second choice*
Antibiotics are not needed in all patients presenting with exacerbations of COPD		
Endorsement	cloxacillin	ceftriaxone/cefotaxime cefazolin clindamycin amoxicillin + clavulanic acid

Committee recommendations

The Expert Committee endorsed the inclusion of cloxacillin (with a square box) as first-choice therapy for empirical treatment of bone and joint infections and of ceftriaxone, cefotaxime, cefazolin, clindamycin, and amoxicillin + clavulanic acid as second-choice therapy. All inclusions apply to both the EML and EMLc.

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Febrile neutropenia

Applicant(s)

McMaster group

Introduction

(description of the condition infecting organisms/public health need)

Febrile neutropenia is a severe infectious syndrome needing empirical treatment in immunocompromised patients.

Summary of evidence (from the application)

One systematic review compared various beta-lactam regimens for empirical treatment of febrile neutropenia (33 randomized controlled trials (RCTs); 4242 participants) and found that cefepime was associated with higher all-cause mortality than other beta-lactams at 30 days (relative risk (RR) 1.44; 95% confidence interval (CI) 1.06–1.94) (*1*). Carbapenems were associated with significantly more frequent adverse events, specifically pseudomembranous colitis (RR 1.94; 95% CI 1.24–3.04; 2025 participants) but with fewer treatment modifications, which is considered a negative outcome. Piperacillin + tazobactam gave rise to a lower rate of adverse events than comparators (RR 0.25; 95% CI 0.12–0.53). A more recent Cochrane review (44 RCTs; 3471 participants) also found a significantly higher mortality with cefepime compared with other beta-lactams (RR 1.39; 95% CI 1.04–1.86), and also concluded that piperacillin + tazobactam was superior to comparators in terms of mortality (RR 0.56; 95% CI 0.34–0.92) (*2*).

Importantly, the inferiority of cefepime was refuted by a meta-analysis conducted by the U.S. Food & Drug Administration (FDA) (88 trials; 9467 cefepime patients and 8288 comparator patients), which found no difference in mortality rates and confirmed these findings in a patient-level meta-analysis (*3*). However, this trial-level meta-analysis was not specific to febrile neutropenia. There were 24 studies in febrile neutropenia; most of the included studies were conducted in other populations: pneumonia (n = 26), intra-abdominal infections (n = 7), urinary tract infections (n = 7), and others (n = 24).

Another Cochrane review, ranked highest in the application among the systematic reviews comparing different regimens, compared beta-lactam with beta-lactam plus aminoglycoside combination therapy in patients with febrile neutropenia (71 RCTs) (*4*). The authors found similar mortality results for trials comparing the same beta-lactam (alone or in combination with an aminoglycoside) (RR 0.74; 95% CI 0.53–1.06) and those comparing a broad-spectrum beta-lactam with a narrower-spectrum beta-lactam combined with an aminoglycoside (RR 0.91: 95% CI 0.77–1.09). Infection-related mortality was significantly lower with monotherapy (RR 0.80; 95% CI 0.64–0.99), and significantly more adverse events were associated with combination treatment, with a number needed to harm of 4 (95% CI 4–6). Similar findings were reported in a 2003 Cochrane review and a non-Cochrane review from 2002 (*5, 6*).

A 2014 Cochrane review assessed empirical antibiotics for Gram-positive bacteria in febrile

neutropenia (13 RCTs; 2392 patients) (*7*). There was no difference in mortality when a glycopeptide was used as part of the initial regimen (RR 0.82; 95% CI 0.56–1.20) and no difference in treatment failure was noted (RR 1.0; 95% CI 0.79–1.27). In contrast, an older and lower-ranked systematic review noted higher success rates were achieved by adding glycopeptides (odds ratio (OR) 1.63; 95% CI 1.17–2.28) (*8*). There were no differences for mortality outcomes but adverse events were more frequent when glycopeptides were added (OR 4.98; 95% CI 2.91–8.55).

A systematic review of fluoroquinolones in low-risk children with febrile neutropenia (6 RCTs and 4 cohort studies) reported no difference in treatment failure as compared with non-fluoroquinolone antibiotics (RR 1.02; 95% CI 0.72–1.45) (*9*). Inferences were limited, however, given that the definition for treatment failure included antibiotic modification and that study quality was not assessed. Another review compared ciprofloxacin plus a beta-lactam with an aminoglycoside plus a beta-lactam for febrile neutropenia (8 RCTs) in a predominately adult population, and found no significant difference for mortality (OR 0.85; 95% CI 0.54–1.35) but marginally better clinical cure with a fluoroquinolone (OR 1.32; 95% CI 1.0–1.74) (*10*).

Finally, a Cochrane review found no difference in outcomes with oral versus IV antibiotics in patients with febrile neutropenia (excluding leukaemia) who were haemodynamically stable and did not have organ failure, pneumonia, central-line or severe soft-tissue infections (treatment failure RR 0.96; 95% CI 0.86–1.06). However, neither this comparison nor the comparison of mortality rates (RR 0.95, 95% CI 0.54-1.68) met the applicant's definition for non-inferiorityy (*11*).

In summary, there is no role for combining aminoglycosides with beta-lactams in empirical treatment of febrile neutropenia: there is no clinically relevant benefit but an increase in adverse events compared with beta-lactam monotherapy. The highest-ranked systematic review indicates that the same is true for routine use of glycopeptides (e.g. vancomycin) – no benefit in clinical cure but a higher rate of adverse events.

Ciprofloxacin combined with a beta-lactam was found to be marginally superior to beta-lactam/aminoglycoside combinations. However, this is based on evidence published before 2005 when fluoroquinolone resistance had less significance than it has now. While this supports the notion that aminoglycosides should not be used routinely in this patient population, no conclusions can be drawn about the potential benefit of fluoroquinolones in the light of the current epidemiology of fluoroquinolone resistance. Overall, no single agent or regimen was found to be clearly superior to other standard regimens; clinical guidelines therefore guided proposals for inclusion on the EML. The exception was cefepime, which has been shown to be associated with a higher risk of death in several systematic reviews and is thus not considered a candidate for the core or targeted list.

Guidelines (from the application)

The 2010 IDSA guidelines recommend that monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, ceftazidime, a carbapenem (meropenem or imipenem + cilastatin), or piperacillin + tazobactam be used (*12*). Other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen for management of complications, if antimicrobial resistance is suspected or as

alternatives if patients are allergic to beta-lactam antibiotics. Alternatives in case of beta-lactam allergies also include aztreonam.

Empirical treatment for fevers persisting after 4 days of broad-spectrum antibiotics includes empirical antifungals, e.g. echinocandins, voriconazole, amphotericin B (beyond the scope of this review). Ciprofloxacin combined with amoxicillin + clavulanic acid is recommended for oral empirical treatment in low-risk patients.

The National Institute for Health and Care Excellence (NICE) guideline recommends monotherapy with piperacillin + tazobactam (*13*); use of empirical aminoglycosides is discouraged. Antibiotics can be switched to an oral regimen after 48 hours of treatment if the patient is at low risk for developing complications.

The International Pediatric Fever and Neutropenia Guideline recommends monotherapy with an antipseudomonal beta-lactam or a carbapenem as empirical treatment in high-risk paediatric patients (*14*). A second Gram-negative agent or glycopeptide should be added for patients who are clinically unstable, when a resistant infection is suspected, or in a centre with a high rate of resistant pathogens.

Rationale for antibiotic selection (from the application)

Amoxicillin + clavulanic acid plus ciprofloxacin were proposed as core antibiotics for ambulatory low-risk patients presenting with febrile neutropenia. For all other patients, piperacillin + tazobactam, which is supported by all clinical guidelines for both adults and children, was proposed as a core antibiotic.

Cefepime was not proposed for inclusion in the EML; it was felt to be redundant in view of the antibiotics already listed above, and there was concern about potential inferiority in terms of mortality. However, it has a potential role as a carbapenem-sparing agent for other indications and is therefore proposed for inclusion on the preserved list as a niche antibiotic. Colistin, aztreonam, daptomycin, linezolid and tigecycline are all proposed for the preserved list as alternative agents for febrile neutropenia and other indications if none of other antibiotics listed here is deemed appropriate because of resistance or other concerns.

Ceftazidime was not proposed due to redundancy with the availability of piperacillin + tazobactam, and the fact that other alternatives, with indications for several more syndromes, have also been proposed for treatment of febrile neutropenia (e.g. meropenem, fluoroquinolones, aminoglycosides). In terms of carbapenems, only meropenem was proposed. Meropenem, aminoglycosides and vancomycin are to be used only if needed in addition to, or instead of, the first-line regimen, piperacillin + tazobactam. The choice of antibiotic should be based on local epidemiology and presentation of the patient as per the recommendations in the clinical guidelines, e.g. high suspicion for a central-line infection, or a patient presenting in septic shock.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. 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 on the EML and/or EMLc. Gentamicin was excluded. Amikacin was preferred to gentamicin because it is usually more active against Enterobacteriaceae.

Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents. The Expert Committee made recommendations in line with Talcott criteria for risk classification (*15*).

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

Addition indicates new antibiotics not currently on EML/EMLc

	First choice	***Second choice***
Endorsement		
Low risk	amoxicillin + clavulanic acid ciprofloxacin	
High risk		vancomycin IV
Trichomonas vaginalis	Metronidazole (EML)	
Addition		
High risk	piperacillin + tazobactam amikacin	meropenem

Committee recommendations

The Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid, with or without ciprofloxacin, as first-choice therapy in low-risk patients with febrile neutropenia.

The Committee endorsed the inclusion of IV vancomycin and the addition of meropenem (indicated in specific situations in combination with first-line regimens) as second-choice therapy in high-risk patients with febrile neutropenia.

The Committee recommended the addition of piperacillin + tazobactam and amikacin (indicated in specific situations in combination with a recommended beta-lactam agent) as first-choice therapy for high-risk patients with febrile neutropenia.

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Severe acute malnutrition

Applicant(s)

WHO Department of Maternal, Newborn, Child and Adolescent Health

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Introduction

(description of the condition/infecting organisms/public health need)

Severe acute malnutrition (SAM) affects nearly 20 million children under 5 years of age, causing up to 1 million deaths each year as a consequence of increasing susceptibility to death from severe infection (*1*). The most susceptible age for malnutrition is 6–18 months, but it is increasingly recognized that SAM may occur in younger infants (*2*). SAM is classified according to the absence or presence of medical complications (*3*):

- *Uncomplicated SAM:* children who are clinically well without signs of infection or other indication for hospital admission, with a retained appetite ("passed the appetite test"). Retained appetite is regarded as indicating the absence of severe metabolic disturbance. Patients are deemed to be most appropriately managed as outpatients, with ready-to-use therapeutic foods.
- *Complicated SAM:* children who have clinical features of infection, metabolic disturbance, severe oedema, hypothermia, vomiting, severe dehydration, severe anaemia or a lack of appetite, requiring inpatient treatment initially with low-protein milk-based feeds. Children are discharged to continue nutritional management as outpatients when complications have resolved.

The following summary is taken from the review of the available evidence for SAM conducted to inform the WHO Department of Maternal, Newborn, Child and Adolescent Health's review of its existing guidelines.

Summary of evidence (from the application)

A comprehensive search for systematic reviews, meta-analyses, multicentre studies and randomized controlled trials was conducted. Seven studies were included in the final analysis: four systematic reviews and/or meta-analyses (*4–7*) and three double-blind, placebo-controlled trials (*8–10*). The meta-analysis by Million et al. (*7*) found an overall benefit for survival in children with SAM treated with amoxicillin, sufficient to reaffirm 2013 WHO recommendations (which recommend amoxicillin for children with uncomplicated SAM). Current evidence supports administration of amoxicillin 80 mg/kg per day in two divided doses for 7 days to children with SAM in the community setting. For complicated SAM, the evidence supports maintaining the existing recommendation of empirical parenteral benzylpenicillin or ampicillin plus gentamicin, followed by oral amoxicillin once the patient is clinically stable.

Guidelines (from the application)

The application stated that there are significant variations in published international guidelines for the suggested antimicrobial therapies for empirical antimicrobial treatment of complicated SAM, many of which pre-date recent trials.

The 2013 WHO guidelines for treatment of SAM (*3*) make the following recommendations regarding antibiotic treatment of SAM:

- Children with uncomplicated SAM, not requiring to hospital admission and managed as outpatients, should be given a course of oral antibiotic such as amoxicillin (conditional recommendation, low-quality evidence).
- Children who are undernourished but do not have SAM should not routinely receive antibiotics unless they show signs of clinical infection (strong recommendation, low-quality evidence).
- Children admitted with SAM and complications such as septic shock, hypoglycaemia, hypothermia, skin infections or respiratory or urinary tract infections, or who appear lethargic or sickly, should be given parenteral (IM or IV) antibiotics.
- Children admitted with SAM and with no apparent signs of infection and no complications should be given an oral antibiotic.

Rationale for antibiotic selection (from the application)

Alignment with WHO guidelines.

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

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the antibiotics proposed in the application from the WHO Department of Maternal, Newborn, Child and Adolescent Health, and selected first-choice antibiotics for inclusion on the EMLc for this indication in alignment with the WHO guidelines. Second-choice therapies were neither proposed nor recommended.

Recommended first-choice antibiotics for uncomplicated and complicated SAM are reported below.

EML listings

Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice – EMLc	*Second choice*
Endorsement		
Uncomplicated SAM	amoxicillin	
Complicated SAM	benzylpenicillin	
	ampicillin	
	gentamicin	
	amoxicillin	
	amikacin	

Committee recommendations

The Expert Committee endorsed the inclusion on the EMLc of amoxicillin as a first-choice therapy for use in uncomplicated severe acute malnutrition, and of benzylpenicillin or ampicillin and gentamicin followed by amoxicillin as first-choice therapy in use in complicated severe acute malnutrition.

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Proposal from the McMaster Group for a "conserved" antibiotics list – for preservation, niche indications, and last-resort use.

The approach used to develop a list of essential antibiotics was based on infectious syndromes and largely on empirical use, that is, use for suspected infection in the absence of (or pending) microbiological evidence for a specific pathogen. Notable exceptions were endocarditis and bone and joint infections. The concept of a "conserved" list was proposed by the applicant to serve several purposes and the list comprised antibiotics that are positioned here for several different reasons.

One of the most important purposes is *preservation* of certain antibiotics – avoiding their use when there are alternatives that are often safer. In this way, antibiotics proposed for preservation can be kept in reserve until they are really needed for specific circumstances (e.g. patient's intolerance or resistance to core and targeted antibiotics) or for future use when resistance rates to the proposed core and targeted antibiotics are very high. They are thus considered last-resort antibiotics. One example is colistin, which is a polymyxin antibiotic that should be used only for multidrug-resistant organisms, such as extremely multidrug-resistant *Pseudomonas aeruginosa* or *Acinetobacter* spp. Colistin carries a risk of nephrotoxicity and should be used judiciously, that is, under strict medical supervision and only if suitable alternatives are not available. Tigecycline is similar in that it has a relatively broad spectrum of activity, against both Gram-positive and Gram-negative pathogens. However, the FDA issued a boxed warning in 2010 due to concern about an increased risk of death. For this reason, the applicant considered that this should be considered a last-resort antibiotic, to be used only when there is no suitable alternative agent.

Other antibiotics were proposed as "niche" antibiotics in that they should be used only for a narrow range of their clinical uses – niche indications targeting specific resistant pathogens. Linezolid, for example, has broad Gram-positive activity, being active against organisms such as vancomycin-resistant enterococcus (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). Resistance to linezolid can develop but remains low, which is why this antibiotic should be used selectively. Daptomycin also has excellent Gram-positive activity and should be preserved, given that resistance is currently low. Rifampicin, used for non-tuberculous infection as an adjunct therapy for rifampicin-susceptible staphylococcal prosthetic joint infections and for prosthetic valve endocarditis, is also in this category. Chloramphenicol was included as a niche antibiotic for its role in bacterial meningitis and typhoid fever in settings where alternatives are not available. Ertapenem, a carbapenem with a long half-life, finds a niche for once-daily dosing in the outpatient setting, particularly for coverage of pathogens with a degree of resistance against core and targeted antibiotics, e.g. extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. In addition to niche indications, ertapenem should be preserved to avoid development of more widespread resistance to carbapenems.

Cefepime, aztreonam and moxifloxacin, were also on the proposed list of preserved antibiotics in order to prevent the development of further resistance. They generally have a reasonable safety profile and good activity: (cefepime, a fourth-generation cephalosporin, has excellent Gram-negative activity; aztreonam has good Gram-negative activity, especially against *Pseudomonas aeruginosa*; and moxifloxacin has the activity expected of a respiratory fluoroquinolone. However, other antimicrobials offer similar coverage, meaning that these antibiotics could be preserved for use only if existing agents become ineffective.

The table below summarizes the proposals for the conserved antibiotic list from the McMaster Group application

Antibiotic	*Systematic reviews*	*Clinical practice guidelines*	*Currently listed on EML/EMLc*	*Proposed list*
linezolid	X	√	X	Niche
tigecycline	X	√	X	Last resort
cefepime	X	√	X	Preserved
colistin	X	√	X	Last resort
daptomycin	X	√	X	Niche
moxifloxacin	X	√	X	Preserved
aztreonam	X	√	X	Preserved
rifampicin	X	√	X	Niche
ertapenem	X	√	X	Niche/preserved
chloramphenicol	X	X	√	Niche

Expert Committee considerations and recommendations: the EML Reserve antibiotics group

The Expert Committee considered the various antibiotics proposed in the McMaster application for conservation, and adapted that list to create the EML Reserve antibiotics group, choosing to focus only on "last-resort" antibiotics or antibiotic classes, to be used when all other alternatives have failed. The Reserve group was identified to improve targeted access according to available recommendations and to reduce the risk of selection of resistance to these last-resort antibiotics.

The Expert Committee excluded moxifloxacin and ertapenem from this group, as fluoroquinolones and carbapenems are already included in the Watch group, and meropenem was recommended as a second-choice treatment for a small number of serious infections. Rifampicin and chloramphenicol were not included in the Reserve list as they were not considered by the Expert Committee to fit the definition of last-resort antibiotics.

The Expert Committee considered the Reserve group should include 4th-generation cephalosporins as a class (not just cefepime), as well as 5th-generation cephalosporins. Other antibiotic classes recommended were polymyxins (to include both colistin and polymyxin B), and oxazolidinones (capturing linezolid and others). The Expert Committee also recommended including IV fosfomycin in the Reserve group and agreed that inclusion of aztreonam, tigecycline and daptomycin on the Reserve group was appropriate. The Committee thus listed the antibiotics of the Reserve ("last resort") group as follows:

Reserve group ("last resort") antibiotics
aztreonam
4th-generation cephalosporins, e.g. cefepime
5th-generation cephalosporins, e.g. ceftaroline
Polymyxins, e.g. polymyxin B, colistin
fosfomycin (IV)
Oxazolidinones, e.g. linezolid
tigecycline
daptomycin

The Reserve group antibiotics should be accessible when needed, but their use should be tailored to highly specific patients and settings, when other alternatives have failed (e.g. serious life-threatening infections due to multidrug-resistant bacteria). To preserve their effectiveness, these medicines could be protected and prioritized as key targets of high-intensity national and international stewardship programmes involving monitoring and utilization reporting.

6.2.2: Other antibacterials

Azithromycin - change: new indication - EML and EMLc

Azithromycin **ATC Code: J01FA10**

Proposal

The application proposed an additional indication for azithromycin on the core list of the EML and EMLc for use in the treatment of yaws.

Applicant(s)

Dr Oriol Mitjà, Ms Laia Bertran – Barcelona Institute for Global Health, Barcelona, Spain

WHO technical department

Department of Control of Neglected Tropical Diseases

EML/EMLc

EML and EMLc

Section

6.2.2 Other antibacterials

Dose form(s) and strength(s)

Tablet and capsule: 250 mg, 500 mg

Oral liquid: 200 mg/5 mL

Core/Complementary:

Core

Individual/Square box listing

Individual

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

Azithromycin is currently available on the EML and EMLc only for single-dose treatment of genital *Chlamydia trachomatis* and of trachoma.

Public health relevance (burden of disease)

Yaws is an infectious, neglected tropical disease (NTD) caused by the *Treponema pallidum pertenue* bacterium. It gives rise to disfiguring cutaneous and skeletal lesions and is spread by skin-to skin-contact. It primarily affects children living in warm, humid, tropical and impoverished areas (*1*).

The WHO Global Health Observatory data repository reported 13 low- and middle-income countries as being endemic for yaws in 2013 (*2*). A 2015 systematic review of 27 studies calculated the prevalence of active yaws to range from 0.31% to 14.54% in endemic areas, while the prevalence of latent disease ranged from 2.45% to 31.05%. In the four years to 2013, 256 343 cases were reported, with over 80% from just three countries – Ghana, Papua New Guinea and Solomon Islands (*3*).

In 2012, WHO revised its global eradication policy for yaws and developed the "Morges Strategy" with the goal of eradicating the disease by 2020 (*4*). New mass drug administration policies were recommended, involving total community treatment and total targeted treatment with oral azithromycin or injected benzathine benzylpenicillin to capture cases and all contacts and achieve rapid interruption of transmission, leading to eradication. It has been estimated that for each clinically apparent case of yaws, up to six latent cases may exist. Treatment of active cases only has been shown to have limited impact on prevalence after 12 months. In contrast, mass drug administration campaigns have achieved a rapid drop in prevalence (*5*).

Summary of evidence – benefits (from the application)

Single-dose azithromycin was shown to be non-inferior to single-dose IM benzathine benzylpenicillin in the treatment of yaws in two recent open-label randomized trials (*6, 7*).

In a trial in 250 children in Papua New Guinea, a single oral dose of azithromycin 30 mg/kg (up to 2 g) produced clinical and serological cure of yaws in 96.4% of cases, compared with 92.2% for IM benzathine benzylpenicillin 50 000 U/kg (risk difference (RD) –3.4%; 95% confidence interval (CI) –9.3 to 2.4) and met the prespecified criteria for non-inferiority (*6*). A similar trial in Ghana involving 353 children yielded similar results. Clinical cure of yaws at 3 weeks was achieved in 98.2% and 96.6% of patients treated with azithromycin and benzathine benzylpenicillin respectively (RD –1.3; 95% CI –4.7 to 2.0) and serological cure at 6 months in 57.5% and 49.1% respectively (RD –8.3; 95% CI –19.1 to 2.4). The prespecified non-inferiority criteria were also met in this study (*7*).

Efficacy of a mass drug administration approach was investigated in a study of 16 092 residents of rural Papua New Guinea (*8*), 83% of whom were treated with single-dose azithromycin and monitored for one year. The prevalence of active yaws fell by 2.1 percentage points from 2.4% to 0.3% (95% CI 1.9–2.4), and the prevalence of latent yaws with high-titre seroreactivity in children fell by 11.8 percentage points from 18.3% to 6.5% (95% CI 8.9–14.7). The effect was most notable in children aged 1–5 years, with high-titre seroreactivity in this subgroup close to zero one year after treatment.

A study conducted in a target population of 15 310 people in Ghana (*9*) also found reduced prevalence of polymerase chain reaction (PCR)-positive active yaws from 3.1% to 0% (95% CI 2.1–4.4) and of latent yaws from 10.7% to 2.1% (95% CI 6.6–10.9) one year after mass treatment with azithromycin. This study was in press at the time of writing.

Cross-sectional surveys in Ghana and the Solomon Islands assessed the impact on yaws of azithromycin mass drug administration for trachoma (*10, 11*). Each found benefit in terms of ongoing transmission of yaws or post-treatment prevalence of yaws.

Summary of evidence – harms (from the application)

No severe adverse events attributable to azithromycin were identified by means of passive surveillance during a large longitudinal study of 13 490 participants given single-dose azithromycin 30 mg/kg in a mass drug administration for yaws. Active surveillance of 316 participants from 60 households found 54 (17.1%) who reported adverse events (all mild), including 30 (9.5%) with nausea or abdominal pain, 25 (7.9%) with diarrhoea, and 15 (4.7%) with vomiting (*8*).

Additional evidence (not in the application)

N/A

WHO guidelines

Azithromycin given orally is preferred to benzathine benzylpenicillin for the treatment of yaws. The recommended dosage is 30 mg/kg body weight (maximum 2 g) as a single dose by mouth. For children aged under 6 years, syrup is preferable; if this formulation is not available, a tablet should be crushed and mixed with water.

Benzathine benzylpenicillin is still effective and relevant in yaws treatment and eradication. Given the operational and logistic problems associated with its administration, however, it may be used as a back-up for people who cannot be treated with, or fail on, azithromycin or in large-scale treatment in places where azithromycin is not available. The standard doses are 0.6 million units for children aged under 10 years and 1.2 million units for people aged 10 years and over.

Costs/Cost–effectiveness

The application presented a comparison of costs for benzathine benzylpenicillin and azithromycin for yaws based on WHO recommended doses. Taking into account non-drug costs associated with administration of benzathine benzylpenicillin, azithromycin was found to be the cheaper option for the age groups 6–9 and 10–15 years. The application claimed that administration of penicillin is more expensive, requiring more highly trained personnel to administer injections.

The application also stated that costs related to acquisition and administration of low-cost generic azithromycin formulations are highly competitive, which offers scope for negotiation of lower prices at country procurement level.

Availability

Azithromycin is widely available, in many generic versions.

Other considerations

The WHO NTD department strongly supported the application and the inclusion of azithromycin on the EML and EMLc for the treatment of yaws, stating that it is in line with, and will significantly contribute to, the WHO "Morges Strategy" for yaws eradication.

Committee recommendations

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.

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6.2.4. Antituberculosis medicines

Clofazimine - change: new indication - EML and EMLc

Clofazimine **ATC Code: J04BA01**

Proposal

The application requested the addition of clofazimine to the Complementary List of the EML and EMLc as a reserve second-line drug for the treatment of multidrug-resistant tuberculosis.

Applicant(s)

Dennis Falzon, Tiziana Masini, Ernesto Jaramillo, WHO Global TB Programme (WHO/GTB) supported by Dr Kaspars Lunte, Global Drug Facility (GDF)

WHO technical department

Global TB Programme

EML/EMLc

EML and EMLc

Section

6.2.4 Antituberculosis medicines

Dose form(s) and strength(s)

Capsule: 50 mg, 100 mg

Core/Complementary

Complementary

Individual/Square box listing:

Individual

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

Clofazimine is already listed in the EML and EMLc for the treatment of leprosy (Section 6.2.3). This request was for an extension of indication to include treatment of multidrug-resistant tuberculosis (MDR-TB) in adults and children. Clofazimine is the only core second-line medicine for the treatment of MDR-TB not yet included in the EML as an antituberculosis agent.

The 2016 update of the WHO treatment guidelines for drug-resistant tuberculosis positions clofazimine as a core second-line (Group C) medicine. Clofazimine may be included as part of both shorter MDR-TB regimens and longer regimens for multidrug- and extensively drug-resistant TB (XDR-TB) (*1, 2*).

Public health relevance (burden of disease)

It is estimated that there are 580 000 new cases of rifampicin- and multidrug-resistant TB (RR-/MDR-TB) worldwide annually and about 250 000 deaths due to the disease. Approximately half of MDR-TB cases globally have also lost susceptibility to key drugs in the MDR-TB regimen (fluoroquinolones, second-line injectable agents, or both) i.e. have become XDR-TB (*3*).

In 2015, countries reported that about 125 000 MDR/RR-TB patients and more than 7000 XDR-TB patients started treatment. Outcome reporting data show that approximately half of all treated MDR-TB patients successfully complete treatment (*4*)

The complexity, duration, toxicity, cost and unavailability of the drug regimens for MDR-TB treatment are a substantial impediment to global scale-up of curative services. Simplifying regimens for patients and providers is a priority. Clofazimine has an important role in shorter MDR-TB regimens and is less costly than the typical medicines used in 24-month MDR-TB regimens.

Summary of evidence – benefits (from the application)

A review of the available evidence for efficacy and safety was undertaken for the 2016 update of the WHO policy for the treatment of MDR-TB (*2*). GRADE tables for the use of clofazimine are presented in Annex 2a of the application (adults), Annex 2b (children) and Annex 2c (clofazimine-containing shorter MDR-TB regimen) and are summarized below.

Clofazimine in adults

One small randomized controlled trial (RCT; 105 patients) assessed treatment success compared with treatment failure or death in non-XDR, MDR-TB patients (*5*). There was a non-statistically significant absolute benefit of 200 more treatment successes per 1000 patients treated with clofazimine (95% confidence interval (CI) 60 fewer to 450 more treatment successes). The relative effect of treatment was not estimable and the quality of evidence was assessed as moderate.

An analysis of six studies in MDR/XDR-TB patients (1 RCT; 5 cohorts) found a non-statistically significant absolute benefit of 10 fewer treatment successes per 1000 patients treated with clofazimine (95% CI 210 fewer to 170 more treatment successes) (*6*). The relative effect of treatment was not estimable and the quality of evidence was assessed as very low.

An individual patient meta-analysis of 31 observational studies assessed treatment success versus failure/relapse/death in MDR-TB patients and found a non-statistically significant benefit of clofazimine treatment (adjusted odds ratio (OR) 1.4; 95% CI 0.4–4.0; absolute benefit 10 more treatment successes per 1000 clofazimine-treated patients, 95% CI 220 fewer to 340 more treatment successes) (*6*). The quality of evidence was assessed as very low.

In addition, the application reported the results of a 2013 systematic review of nine observational studies (six MDR-TB, three XDR-TB) (*7*). Overall, 65% (95% CI 54–76) of clofazimine-treated patients achieved either cure or treatment completion. The median number of medicines used in the regimens, including clofazimine, ranged from 4 to 7. Using random-effects meta-analysis the authors concluded that there were favourable treatment outcomes in 65% (95% CI 52–79) of patients with MDR-TB and 66% (95% CI 42–89) of patients with XDR-TB.

A systematic review of 12 studies (3489 patients) evaluated the efficacy and safety of clofazimine as part of combination therapy for drug-resistant TB (*8*). Treatment success ranged from 16.5% (95% CI 2.7–38-7) to 87.8% (95% CI 76.8–95.6), with an overall pooled proportion of 61.96% (95% CI 52.79–71.12) treatment success in clofazimine-treated patients. It was not possible to identify optimal dose and duration of use of clofazimine.

The application noted that the success rates reported by Gopal et al. (*7*) and Dey et al. (*8*) are higher than usually reported in MDR/XDR-TB patients and that the results might be partly explained by the inclusion of heterogeneous treatment regimens, and by biases and residual confounding associated with observational studies.

Clofazimine in children

Individual patient data meta-analysis of 9 observational studies (623 patients) was conducted by Harausz et al. (unpublished, with summary in reference *6*)). It assessed treatment success versus failure/relapse/death in MDR-TB patients and found a non-statistically significant benefit of clofazimine treatment in confirmed MDR-TB cases (adjusted OR 0.46; 95% CI 0.02–10.0; absolute benefit 46 more treatment successes per 1000 clofazimine-treated patients, 95% CI 81 fewer to 170 more treatment successes). The quality of evidence was assessed as very low.

Clofazimine in shorter MDR-TB regimens

A meta-analysis of 37 observational studies used an indirect comparison of two aggregate data meta-analyses of six studies of shorter-duration regimens (preliminary data from three series and data from three published studies) and 31 studies of conventional MDR regimens to assess treatment success versus failure/relapse (*6*). Relative and absolute benefits were not calculated. The data from the two aggregate meta-analyses indicated treatment success in 97.6% of standardized shorter regimens and 86.9% with conventional longer regimens. The quality of the evidence was assessed as very low.

Summary of evidence – harms (from the application)

The application suggested that the adverse event profile for clofazimine is known from its use in the treatment of leprosy.

Annex 2a summarized data on serious adverse events (resulting in drug discontinuation) from studies of the use of clofazimine in adults. Serious adverse event rates in clofazimine-treated patients were 2.5% in MDR/XDR-TB assessed in five comparative observational studies and 12.8% in six uncontrolled observational studies. Event rates were 3.3% in non-tuberculosis mycobacterium (NTM) assessed in four comparative observational studies (*6*). The quality of all data was assessed as very low.

A meta-analysis of five observational studies involving 861 patients, of whom 602 received clofazimine as part of their TB treatment, found the overall proportion of patients with adverse drug reactions (ADRs) to be 21.9% (95% CI 0.0–46.1), while the proportion of patients with ADRs requiring discontinuation of clofazimine was 0.1% (95% CI 0.0–0.6) (*9*).

There are few data on adverse event rates in children. The applicationreported that 75–100% of patients develop orange–red skin pigmentation which is usually reversible months to years after cessation of treatment. Discolouration of conjunctiva, cornea and body fluids also occurs. Less common ADRs include maculopathy, severe abdominal symptoms, photosensitivity

bleeding, bowel obstruction, prolongation of the QT interval and ventricular tachyarrhythmias. Joint administration of clofazimine with other medicines known to prolong the QT interval (including bedaquiline, fluoroquinolones, delamanid, azole antifungals) may have additive adverse effects.

The application argued: "... despite the fact that clofazimine is associated with several ADRs, WHO and other authorities have since many years considered it to be an essential drug for the treatment of leprosy, a condition which is far less lethal than M/XDR-TB. Treatment of MDR-TB commonly leads to a whole constellation of adverse effects and the majority of patients exposed have at least one event, often requiring a modification of the regimen (*10*). If the addition of clofazimine to a regimen can increase the likelihood of success by 10%, at the expense of a slight increase in non-serious adverse effects, then the balance of risks to benefits may well tip in favour of the latter."

Additional evidence (not in the application)

N/A

WHO guidelines

The 2011 WHO guidelines on MDR/XDR-TB treatment included clofazimine in Group 5 of second-line drugs and recommend its use when other treatment options are not possible (*11*). The 2016 update of the WHO policy for the treatment of MDR-TB now conditionally recommends the use of a shorter MDR-TB regimen in which clofazimine is a mainstay second-line drug used throughout the 9-month treatment duration. In addition, the 2016 WHO treatment guidelines for MDR-TB include clofazimine as one of the four medicines in Group C, making it a core-drug option for conventional 24-month regimens for MDR/XDR-TB (see Table 1 of the application) (*1*).

Costs/Cost–effectiveness

The application provided several indicative prices for clofazimine, valid in June 2016, based on its use to treat leprosy, e.g. US$ 109.48 for 100 capsules of 100 mg; US$ 0.547–0.713 per 50-mg capsule.

Availability

While clofazimine is registered by a number of regulatory agencies (including U.S. Food & Drug Administration, European Medicines Agency, the Australian Therapeutic Goods Administration, Japan, France), it is not registered for the treatment of tuberculosis by any stringent regulatory authority.

Other considerations

N/A

Committee recommendations

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.

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Delamanid - change: new indication - EMLc

Delamanid **ATC Code: J04AK06**

Proposal

The application requested 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 to 17 years.

Applicant(s)

Dennis Falzon, Ernesto Jaramillo and Licé González-Angulo, WHO Global TB Programme supported by Ms Magali Babaley, Global Drug Facility (GDF)

WHO technical department

Global TB Programme

EML/EMLc

EMLc

Section

6.2.4 Antituberculosis medicines

Dose form(s) and strength(s)

Tablet: 50 mg

Core/Complementary

Complementary

Individual/Square box listing

Individual

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

In 2014 WHO issued interim policy guidance on the use of delamanid in adults (*1*). In 2015, the WHO Expert Committee on the Selection and Use of Essential Medicines recommended the inclusion of delamanid on the EML for the treatment of adult patients with multidrug-resistant tuberculosis (MDR-TB) (*2*). Following a review of paediatric data, WHO guidance was extended in 2016 to include the treatment of children and adolescents aged 6–17 years with multidrug- or rifampicin-resistant (MDR/RR-TB) and extensively drug-resistant (XDR-TB) tuberculosis (*3, 4*).

Public health relevance (burden of disease)

Of an estimated 10.4 million incident cases of TB globally in 2015, 1 million occurred in children. It is estimated that there are 580 000 new MDR/RR-TB cases worldwide annually and about 250 000 deaths due to the disease. Many MDR/RR-TB cases, including children, go undetected and are not given appropriate treatment, increasing the risk of death or transmission of drug-resistant strains (*5*).

Delamanid could provide a valuable contribution to MDR-TB and XDR-TB regimens, when a minimum of four effective second-line medicines cannot be ensured or when other factors predispose to an unfavourable outcome. The likelihood of treatment success in MDR-TB patients diminishes with the acquisition of additional resistance and is particularly low in XDR-TB patients.

Summary of evidence – benefits (from the application)

A review of the available evidence for efficacy and safety was undertaken for the 2016 revision of the WHO guidance for use of delamanid in children (*3*). GRADE tables for the use of delamanid in patients aged 6–17 years are presented in Annex 2 of the application and are summarized below.

Data were extrapolated from adults to children from a randomized placebo-controlled trial, an open observational trial and an observational study. Confidential raw data from preclinical studies in children were provided by the Otsuka Pharmaceutical Company. The quality of data available was assessed as very low.

Evidence of benefit from the randomized placebo-controlled trial (RCT)was based on surrogate outcomes: sputum culture conversion (SCC) to negative at 2 months and time to culture conversion at 2 months. The observational study reported both sustained SCC and cure at 24 months.

At 2 months, SCC to negative and time to culture conversion were statistically significantly higher in patients receiving delamanid on top of an optimized second-line treatment regimen (risk ratio (RR) 1.60; 95% confidence interval (CI) 1.18–2.18; and hazard ratio (HR) 0.58; 95% CI 0.39–0.89, respectively).

At 24 months, sustained SCC (after 8 months' treatment) and cure were statistically significantly higher in delamanid-treated patients (RR 1.22; 95% CI 1.09–1.27; and RR 1.35; 95% CI 1.03–1.63, respectively).

Mortality was lower in delamanid-treated patients at 24 months (RR 0.19; 95% CI 0.01–0.77).

Summary of evidence – harms (from the application)

Fewer serious adverse events were reported in the RCT, with no evidence of higher rates of adverse events in delamanid-treated patients (RR 1.23; 95% CI 0.61–2.33).

Exposure to delamanid was associated with a statistically significant increase in QT prolongation in adults and it was considered that this effect could be generalized to under-18-year-olds (QT prolongation over 2 months, RCT, 9.9% vs 8.8%; RR 2.65; 95% CI 1.08–5.99). QT prolongation by more than 60 ms was reported in 7.5% of delamanid-treated

patients compared with no patients receiving an optimized background regimen (odds ratio (OR) 12.81; 95% CI 1.65–99.7).

Acquired resistance to delamanid was not estimable in either the RCT or the open observational trial.

Additional evidence (not in the application)

WHO interim policy recommends that delamanid may be added to a WHO-recommended regimen for patients with pulmonary MDR-TB or XDR-TB disease under five conditions (*3, 4*):

- Delamanid may not be warranted if an effective regimen can be composed with other second-line medicines, but may be justified in patients at high risk of poor outcomes. Because of concerns about corrected QT (QTc) prolongation, children with a QTcF >500 ms should not receive delamanid.
- There are no data on the effectiveness and safety of delamanid when used alongside a WHO-recommended, 9–12-month, shorter MDR-TB regimen and no data on the simultaneous use of bedaquiline and delamanid in children. No recommendation on delamanid use in children younger than 6 years can be made until ongoing studies are completed.
- Supervised treatment should be adapted to twice-daily administration of delamanid.
- Active TB drug safety monitoring is required, particularly for QTc interval prolongation and cardiac dysrhythmias, as is monitoring of electrolyte disturbances (especially potassium).
- Informed consent is obtained from the parent or guardian. The health authority may additionally require that the child/adolescent would also consent to receive delamanid.

WHO guidelines

Table 1 of the application summarized 2016 WHO policy recommendations for the treatment of RR- and MDR-TB. Delamanid is an add-on agent and not part of the core MDR-TB regimen.

Costs/Cost–effectiveness

Since March 2016, a concessional price of US$ 1700 for a 6-month delamanid treatment in adults was announced by the Otsuka Pharmaceutical Company. All countries that are eligible for financing through the Global Fund to Fight AIDS, Tuberculosis and Malaria and that follow WHO guidelines for MDR-TB management in quality-assured programmes could procure delamanid through the Global Drug Facility at this price. Prices in high-income countries are much higher, e.g. £17 500 for a 24-week course in the United Kingdom and about US$ 33 000 for a 6-month course of 100 mg twice daily in Germany.

Availability

Delamanid has marketing authorization in China, Hong Kong Special Administrative Region, Europe, Japan and Republic of Korea.

Other considerations

Not recommended for children <6 years.

Committee recommendations

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.

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Gatifloxacin – rejection – EML and EMLc

Gatifloxacin **ATC Code: J01MA16**

Proposal

The application requested 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.

Applicant(s)

Dennis Falzon, Tiziana Masini, Ernesto Jaramillo, WHO Global TB Programme (WHO/GTB) supported by Dr Kaspars Lunte, Global Drug Facility (GDF)

WHO technical department

Global TB Programme

EML/EMLc

EML and EMLc

Section

6.2.4 Antituberculosis medicines

Dose form(s) and strength(s)

Tablet: 200 mg; 400 mg

Core/Complementary

Complementary

Individual/Square box listing

Individual

Background

(if relevant, e.g. resubmission, previous EC consideration)

The 2016 update of the WHO treatment guidelines for drug-resistant tuberculosis positions gatifloxacin as an alternative to other fluoroquinolones (specifically levofloxacin and moxifloxacin) in Group A. Gatifloxacin may be included as part of both shorter regimens for multidrug-resistant tuberculosis (MDR-TB) and longer regimens for MDR-TB and extensively drug-resistant TB (XDR-TB) (*1, 2*).

Currently, the EML and EMLc include the fluoroquinolone, levofloxacin, for this indication, with an asterisk and a note specifying that ofloxacin and moxifloxacin may be alternatives based on availability and programme considerations. Ofloxacin was proposed for removal

from the Model Lists in a separate application to this meeting on the basis that it is no longer recommended in the updated WHO treatment guidelines.

Public health relevance (burden of disease)

It is estimated that 580 000 patients develop rifampicin-resistant or MDR-TB globally each year and would need second-line TB treatment regimens to increase the likelihood of a successful treatment outcome (*3*). In many low-resource settings, there are often too few medicines available to compose a suitable regimen for drug-resistant TB, and stock-outs of second-line drugs occur regularly (*3*).

Gatifloxacin was a mainstay fluoroquinolone of the shorter MDR-TB regimen until a global shortage of quality-assured formulations of the medicine occurred following safety concerns (*4*). Clinicians had to replace gatifloxacin with other later-generation fluoroquinolones in both shorter and longer MDR-TB regimens. Given that gatifloxacin is cheaper to manufacture than other later-generation fluoroquinolones, the inclusion of gatifloxacin on the EML should encourage pharmaceutical manufacturers to produce this medicine.

Summary of evidence – benefits (from the application)

A review of the available evidence for the effectiveness of, and adverse reactions to, gatifloxacin was undertaken for the 2016 revision of the WHO treatment guidelines for MDR-TB (*1*). The GRADE table of the evidence was presented in Annex 2 of the application and the findings are summarized below.

There are few data on the effectiveness of gatifloxacin in either conventional 24-month MDR-TB regimens or shorter MDR-TB regimens. Four observational studies were presented (*5–8*); all were assessed as being of very low quality. The studies reported treatment success versus failure, relapse or death in gatifloxacin-treated patients versus no gatifloxacin in rifampicin-resistant or MDR-TB. (In the no gatifloxacin group, the other fluoroquinolone used was ofloxacin, levofloxacin or moxifloxacin.) Treatment success was reported as 84% for regimens with gatifloxacin compared with 64.9% for regimens without (relative benefit not estimable; absolute effect 191 more successes per 1000; 95% confidence interval (CI) 116–265).

Deaths among patients treated with gatifloxacin (2.7%) were lower than those in patients who received another fluoroquinolone or no fluoroquinolone (8.6%), suggesting improved outcome rather than any risk of excess mortality in patients exposed to gatifloxacin (relative benefit not estimable; absolute effect 59 fewer per 1000; 95% CI 20–99).

Summary of evidence – harms (from the application)

Safety data were derived from five observational studies (*5, 9–12*). Serious adverse events (Grade 3 or 4 or treatment stopped because of adverse effects) were reported in 3.6% of gatifloxacin-treated patients compared with 8% of patients given treatments that did not include gatifloxacin (relative and absolute effects were not estimable). Adverse events are likely to be incompletely reported in some of the studies included in the review.

Reports of blood glucose disorders in patients treated with gatifloxacin for conditions other than drug-resistant TB led the manufacturer to stop production of the drug in 2006 (*4*). Reports of severe dysglycaemia, hypoglycaemia and hyperglycaemia and diabetes led to some countries removing gatifloxacin from their national formularies. A global shortage in quality-assured formulations of this medicine ensued, with consequent negative impacts on MDR-TB treatment regimens that included gatifloxacin. More recent reports of treatment regimens for drug-susceptible TB that included gatifloxacin (400 mg once daily) have shown no significant risk of hyperglycaemia associated with exposure (*13*).

Additional evidence (not in the application)

N/A

WHO guidelines

The application suggested that gatifloxacin could be an important component of both the intensive and the continuation phase of the shorter MDR-TB regimen recommended by WHO (*1, 2*). The regimen is usually composed of pyrazinamide, ethambutol, isoniazid, gatifloxacin (or moxifloxacin), kanamycin (or amikacin), protionamide (or ethionamide) and clofazimine for 4 months (extended to 6 months in case of failure of sputum conversion), followed by a continuation phase of pyrazinamide, ethambutol, gatifloxacin (or moxifloxacin), and clofazimine for 5 months. Since May 2016, WHO has recommended the shorter MDR-TB regimen in selected patients; gatifloxacin could thus have a central role in a regimen that is offered to patients as a standard of care unless they have specific exclusion criteria. Moreover, gatifloxacin could be the fluoroquinolone of choice for the longer regimens for both MDR-TB and XDR-TB, which are usually composed of pyrazinamide plus at least four second-line anti-TB drugs considered to be effective, including a later-generation fluoroquinolone, a second-line injectable, and two or more of: ethionamide (or protionamide), cycloserine, linezolid or clofazimine.

In August 2012, WHO advised countries to introduce shorter MDR-TB regimen only under operational research conditions, subject to the approval of a national ethics review and with an appropriate assessment of the effectiveness and safety of treatment. In May 2016, following a review of evidence that accrued from such studies, WHO conditionally recommended the use of a shorter MDR-TB regimen under normal programmatic conditions in patients who fulfil the eligibility criteria for this treatment.

Costs/Cost–effectiveness

A restart of the manufacture of quality-assured formulations of the medicine could substantially lower the costs of TB treatment regimens by substituting for more expensive fluoroquinolone options.

Availability

Generic manufacturers in India and Bangladesh are known to produce gatifloxacin tablets for export; however, these manufacturers are not yet quality-assured. In October 2016,

WHO added gatifloxacin to the list of anti-TB medicines for which manufacturers will be invited to submit an Expression of Interest for Active Pharmaceutical Ingredient (API) or Finished Pharmaceutical Products to the WHO Prequalification Team. It is expected that a number of manufacturers will respond to this invitation.

Other considerations

Listing of gatifloxacin was proposed as an alternative fluoroquinolone to levofloxacin and moxifloxacin which are already included as reserve second-line medicines on the EML and EMLc.

With the recommended deletion of ofloxacin, separate EML listings could be considered for fluoroquinolones recommended as Group A alternatives in the updated WHO guidelines.

Committee recommendations

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).

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Isoniazid + pyrazinamide + rifampicin – change: new formulation – EMLc
Isoniazid + rifampicin – change: new formulation – EMLc

Isoniazid + pyrazinamide + rifampicin **ATC Code: J04AM05**
Isoniazid + rifampicin **ATC Code: J04AM02**

Proposal

The application requested addition to the core list of the EMLc of two fixed-dosecombination, child-friendly formulations for the treatment of children less than 25 kg with tuberculosis in the intensive phase (isoniazid + pyrazinamide + rifampicin) and the continuation phase (isoniazid + rifampicin).

Applicant(s)

Dr Malgorzata Grzemska, Dr Kefas Samson and Ms Annemieke Brands, WHO Global TB Programme

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WHO technical department

Global TB Programme

EML/EMLc

EMLc

Section

6.2.4 Antituberculosis medicines

Dose form(s) and strength(s)

Isoniazid + pyrazinamide + rifampicin: tablet (dispersible) 50 mg + 150 mg + 75 mg

Isoniazid + rifampicin: tablet (dispersible) 50 mg + 75 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

A fixed-dose combination (FDC) of rifampicin 60 mg + isoniazid 30 mg + pyrazinamide 150 mg was added to the EMLc in 2007. In making its recommendation, the Expert Committee considered that this formulation was probably useful for many children but noted that there was no clinical evidence for any FDCs in children and requested that a review of clinical evidence be undertaken (*1*). In 2009, this FDC was deleted from the EMLc after

the Expert Committee found it to be associated with a potential for underdosing and risk of treatment failure (*2*). The Expert Committee noted that pharmacokinetic simulations identified FDCs that were likely to produce systemic exposure of appropriate efficacy and safety in children, but that the formulations proposed were not available at that time and so could not be evaluated. Until now, no such applications had been received for Expert Committee evaluation.

Currently, there are no FDCs on the EMLc for the treatment of children with tuberculosis. FDCs containing isoniazid, pyrazinamide and rifampicin in different strengths from those proposed in the current application are included on the EML.

Isoniazid, pyrazinamide and rifampicin are all available individually on the EMLc in both solid and liquid dose forms.

Public health relevance (burden of disease)

According to the 2016 WHO Global TB Report, at least 1 million children become ill with tuberculosis each year. In 2015, 210 000 died as a result of tuberculosis, including 40 000 children coinfected with HIV. It is reported that children represent approximately 10% of all tuberculosis cases annually (*3*).

Summary of evidence –benefits (from the application)

Evidence for the clinical effectiveness of isoniazid, pyrazinamide and rifampicin was evaluated at the time of their individual listings.

The proposed FDCs contain doses of the component medicines in ratios consistent with the most recent WHO recommendations (ratio of isoniazid to rifampicin of 2 : 3) (*4*). Pharmacokinetic studies of the WHO-recommended doses in children under 2 years of age have shown serum drug concentrations within the recommended therapeutic range (*5*).

Oral bioavailability studies conducted by the manufacturer found that the FDCs were bioequivalent to the relevant reference products in tests conducted in healthy, fasting adults. These studies also concluded that the FDC formulations were well tolerated following single dose administration. The study reports are confidential.

Summary of evidence – harms (from the application)

Evidence for the safety of isoniazid, pyrazinamide and rifampicin was evaluated at the time of their individual listings.

Additional evidence (not in the application)

N/A

WHO guidelines

In 2014, WHO updated its *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (*4*). The recommended dosages of anti-TB medicines for treatment of children are:

- isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day

- rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
- pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg)

(Strong recommendation, moderate quality evidence).

The guidance states that, as children approach a body weight of 25 kg, adult dosing recommendations may be used.

Evidence summary tables supporting the recommendations made in the 2014 WHO Guidance are presented in Annex 1 of the application, and are available on the WHO website at: http://www.who.int/tb/publications/Evidence_tables.pdf (pages 28–38).

Costs/Cost–effectiveness

The cost of treatment ranges from US$ 5.18 to US$ 20.72 depending on the weight band and dose administered.

Availability

Macleods Pharmaceuticals Ltd, India

Global TB Drug Facility (United Nations Office for Project Services)

Other considerations

The formulations have been submitted for WHO prequalification but did not have prequalified status at the time of writing.

Committee recommendations

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.

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Ofloxacin – deletion – EML and EMLc

Ofloxacin	ATC Code: J01MA01

Proposal

The application requested 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 (MDR-TB).

Applicant(s)

Dennis Falzon, WHO Global TB Programme

WHO technical department

Global TB Programme

EML/EMLc

EML and EMLc

Section

6.2.4 Antituberculosis medicines

Dose form(s) and strength(s)

Not specified in the current Model Lists. Rather, ofloxacin is referred to in a note with the listing of levofloxacin (see Background).

Core/Complementary

Complementary

Individual/Square box listing

Shown as alternative to levofloxacin.

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

Ofloxacin is currently included on the EML and EMLc as a potential alternative to levofloxacin for treatment of multidrug-resistant tuberculosis (MDR-TB), based on availability and programme considerations. Ofloxacin does not have an individual listing for this indication.

Public health relevance (burden of disease)

It is estimated that 580 000 patients develop rifampicin-resistant or MDR-TB globally each year and would need second-line TB treatment regimens to increase the likelihood of a successful treatment outcome (*1*).

Summary of evidence – benefits (from the application)

In May 2016, the WHO Global TB Programme revised its guidance for the treatment of drug-resistant tuberculosis (*2*). As a result, a reclassification of medicines for inclusion in regimens for rifampicin-resistant TB (RR-TB) or MDR-TB was recommended. The new guidance no longer includes ofloxacin among the recommended fluoroquinolone options. This is because the other members of the fluoroquinolone class listed (levofloxacin, moxifloxacin and gatifloxacin) are more effective than ofloxacin in second-line TB regimens. The three fluoroquinolones now recommended have become more widely available and affordable globally in recent years.

No specific data were provided in the application.

Summary of evidence – harms (from the application)

No specific data were provided in the application.

Additional evidence (not in the application)

The online appendices for the 2016 WHO MDR-TB guidelines provide a summary of the evidence for use of later-generation fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) compared with ofloxacin for adults with RR-TB or MDR-TB (*3*).

Ahuja et al. (*4*) used individual patient data meta-analyses from 32 observational studies that assessed treatment success versus failure/relapse/death in patients on later-generation fluoroquinolones or ofloxacin as part of an MDR-TB regimen. Treatment success was reported as 83% for regimens with later-generation fluoroquinolones compared with 73.2% for regimens including ofloxacin (odds ratio (OR) 1.9; 95% confidence interval (CI) 1.0–3.6) (low-quality evidence).

Serious adverse events attributable to fluoroquinolones have been reported as 2.8% (95% CI 1.9–4.1%) with ofloxacin or ciprofloxacin, compared with 1.2% (95% CI 0.6–2.4%) for other fluoroquinolones (*2*).

WHO guidelines

The 2016 WHO guidelines (*2*) state the following in reference to the treatment of MDR-TB and RR-TB:

"In patients with RR-TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C (conditional recommendation, very low certainty in the evidence). If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.

In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence)."

Recommended medicines by groupings are as follows:

- Group A: fluoroquinolones – levofloxacin, moxifloxacin, gatifloxacin
- Group B: second-line injectables – amikacin, capreomycin, kanamycin, streptomycin
- Group C: other core second-line agents: ethionamide/protionamide, cycloserine/terizidone, linezolid, clofazimine
- Group D: add-on agents (not part of the core MDR-TB regimen)
  - D1: pyrazinamide, ethambutol, high-dose isoniazid
  - D2: bedaquiline, delamanid
  - D3: *p*-aminosalicylic acid, imipenem + cilastatin, meropenem, amoxicillin + clavulanic acid, thioacetazone.

Costs/Cost–effectiveness

N/A

Availability

N/A

Other considerations

N/A

Committee recommendations

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.

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Streptomycin – deletion – EML

Streptomycin **ATC Code: J01GA01**

Proposal

The application requested deletion of streptomycin as a first-line anti-tuberculosis medicine from the core list of the EML.

Applicant(s)

Malgorzata Grzemska, WHO Global TB Programme.

WHO technical department

Global TB Programme

EML/EMLc

EML

Section

6.2.4 Antituberculosis medicines

Dose form(s) and strength(s)

Powder for injection: 1 g (as sulfate) in vial

Core/Complementary

Removal from core list only

Individual/Square box listing

Individual

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

Streptomycin is currently included in the core list of the EML under Section 6.2.4 for first-line treatment of tuberculosis. It is also included in the Complementary List of the EML and EMLc as a reserve second-line drug for multidrug-resistant tuberculosis (MDR-TB).

Public health relevance (burden of disease)

Not provided

Summary of evidence – benefits (from the application)

In February 2017, the WHO Guidelines Review Committee approved the new WHO *Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update* (in press). The updated guidelines no longer recommend the use of streptomycin as a

component of first-line antituberculosis therapy but reserve its use as a potential option in second-line regimens for drug-resistant disease.

Summary of evidence – harms (from the application)

Not provided

Additional evidence (not in the application)

N/A

WHO guidelines

Refer to the summary for deletion of ofloxacin for recommendations regarding the use of streptomycin in MDR-TB and rifampicin-resistant (RR-TB) disease in current WHO guidelines.

Costs/Cost–effectiveness

N/A

Availability

N/A

Other considerations

The current listing of streptomycin on the Complementary List of the EML and EMLc as a reserve second-line drug for treatment of MDR-TB will be retained.

Committee recommendations

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 – EML and EMLc

Itraconazole **ATC Code: J02AC02**

Proposal

The application requested addition of itraconazole to the core list of the EML and EMLc for treatment of chronic cavitary pulmonary aspergillosis, invasive 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.

Applicant(s)

Global Action Fund for Fungal Infection, Geneva, Switzerland, in association with the International League of Dermatological Societies, Manchester University, Manchester, England, and the Medical Mycology Reference Laboratory of the Instituto de Salud Carlos III, Madrid, Spain

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WHO technical department

N/A

EML/EMLc

EML and EMLc

Section

6.3 Antifungal medicines

Dose form(s) and strength(s)

Capsule: 100 mg

Oral liquid: 10 mg/mL

Core/Complementary

Core

Individual/Square box listing

Individual

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

Itraconazole was considered for inclusion on the EML and EMLc by the Expert Committee in 2015 and was not recommended. The Committee considered that itraconazole could

be interpreted to be an eligible alternative agent within the existing square box listing of fluconazole.

The Expert Committee accepted the role of itraconazole in the treatment of a wide range of fungal infections, including some for which fluconazole is ineffective, such as aspergillosis. The Committee noted that itraconazole demonstrated similar efficacy to fluconazole for many indications but is inferior to other antifungal agents in other settings (e.g. induction and maintenance therapy for cryptococcal meningitis). Further, the Committee noted that the capsule and oral solution formulations were not interchangeable and dosing recommendations differed in relation to food. The Committee also noted the large number of significant drug–drug interactions associated with itraconazole and the use of therapeutic drug monitoring for those with life-threatening infections (*1*).

Public health relevance (burden of disease)

Chronic pulmonary aspergillosis (CPA) is estimated to affect more than 3 million people worldwide, of whom approximately 1.2 million have had tuberculosis (*2*). Following pulmonary tuberculosis, 25–33% of patients are left with residual cavitation in the lung and, of these, 10–35% develop CPA. Five-year survival without antifungal treatment is approximately 20% (*3, 4*).

It is estimated that more than 200 000 people develop *acute invasive aspergillosis* annually (*5*). The disease is common in people with acute leukaemia, those who have haematopoietic stem cell transplantation (HSCT) and other transplant recipients (*6*). Less commonly, invasive aspergillosis occurs in people receiving corticosteroids for many reasons including chronic obstructive pulmonary disease (>1.2% of admissions to hospital), lung cancer and autoimmune disorders (such as systemic lupus erythematosus) (*7*). Other significant risk factors include medical intensive care, liver failure and severe burns (*8*). However, as some of these conditions are more prevalent than haematological cancer and transplantations, the number of individuals with invasive aspergillosis may be higher than estimated. Mortality without antifungal treatment is 100%.

Disseminated *histoplasmosis* is the most common opportunistic infection of newly presenting AIDS patients in parts of Latin America and is a fatal infection if untreated (*9*). Other at-risk groups include those at the extremes of age and the immunosuppressed. Chronic cavitary histoplasmosis is a rare complication of histoplasmosis for which patients with chronic obstructive pulmonary disease are at risk (*10*).

Sporotrichosis has been reported worldwide but most cases occur in central and south America and China (*11, 12*) with rates of 1 case per 1000 in hyperendemic rural areas. The infecting fungus, *Sporothrix schenckii,* usually enters the body by traumatic implantation. Disease may become disseminated in patients with AIDS.

Paracoccidioidomycosis is endemic to Latin America; there are estimated to be fewer than 10 000 cases worldwide annually (*13*). Risk of more severe infection is associated with AIDS and smoking. There is a high rate of coinfection with tuberculosis (*11, 14*).

Systemic mycoses due to *T. marneffei* infection in patients with AIDS present all over the world. It has been estimated that approximately 10% of AIDS patients in China, Hong Kong Special Administrative Region, and around 30% of AIDS patients in northern Thailand are affected (*15*). The infection is known to affect other immunocompromised patients and is

potentially fatal if untreated (*16*).

Chromoblastomycosis is characterized by proliferating, chronic, disfiguring skin lesions. The highest prevalence of the disease is in tropical and subtropical climates. Incidence rates up to 14/100 000 have been reported.

Summary of evidence – benefits (from the application)

The application presented the outcomes of various prospective studies of itraconazole by indication (refer to Tables 3 to 9 of the application).

Chronic pulmonary aspergillosis (17–19)

A small randomized controlled trial (RCT) compared itraconazole with supportive therapy in 31 patients with chronic cavitary pulmonary aspergillosis (*18*). Response to therapy was assessed clinically, radiologically and overall following 6 months of therapy. Overall response was 76.5% in the itraconazole group versus 35.7% in the standard care group. The difference was statistically significant ($P = 0.02$). The percentage of patients showing clinical and radiological response were also higher in the itraconazole group.

Acute invasive aspergillosis (20, 21)

A multicentre prospective, uncontrolled study investigated oral itraconazole in 76 evaluable patients with various underlying conditions (*21*). Response was assessed on the basis of clinical and radiological criteria and categorized as complete, partial or stable. Treatment duration varied from 0.3 to 97 weeks. At the end of treatment, complete/partial or stable responses were observed in 39% and 4% of patients, respectively. Therapy was discontinued in 26% of patients because of clinical worsening or death due to aspergillosis; 30% of patients withdrew for other reasons (toxicity, death from other causes). Itraconazole failure rates varied widely according to site of disease and underlying disease group and were as high as 44% in AIDS patients.

Histoplasmosis

Two studies evaluated itraconazole for treatment of histoplasmosis (*22, 23*). Treatment success was observed in over 80% of patients in both studies.

In an RCT of itraconazole versus placebo for prophylaxis, histoplasmosis developed in 2.7% of patients in the itraconazole group versus 6.8% of patients given placebo ($P = 0.03$) (*24*). In general, 19.5% of patients in the itraconazole group developed a fungal opportunistic infection compared with 28.8% in the placebo group ($P = 0.004$). Prophylaxis significantly reduced the incidence of histoplasmosis ($P = 0.02$; log-rank test) and all invasive fungal infections ($P = 0.0009$; log-rank test) in patients with CD4 counts <100/mm3.

Sporotrichosis

Three prospective, uncontrolled multi-centre studies evaluated itraconazole in patients with cutaneous, systemic and lymphangitic sporotrichosis (*25–27*). High or complete response to itraconazole was reported in all three studies.

Paracoccidioidomycosis

A retrospective cohort study compared itraconazole with sulfamethoxazole + trimethoprim (SMX-TMP) in 200 patients with mild or moderate paracoccidioidomycosis (*28*). There was a higher incidence of response with itraconazole than with SMX-TMP, with cure rates of

86.4% and 51.3%, respectively. In addition, the median treatment period for itraconazole was significantly shorter than for SMX-TMP: 12 months and 23 months, respectively. A Cox proportional hazard regression model showed that use of itraconazole increased the hazard of cure compared with the use of the SMX–TMP.

Mycoses caused by T. marneffei

In a prospective, uncontrolled trial in 74 HIV-infected patients with disseminated *T. marneffei* infection, treatment with IV amphotericin B for 2 weeks, followed by 10 weeks of oral itraconazole was associated with a 97.3% response to treatment (*29*).

Itraconazole for primary prophylaxis was compared with placebo in an RCT of 129 patients infected with HIV (*30*). Results from the intent-to-treat analysis showed development of systemic fungal infection (*T. marneffei*) in 1.6% of the itraconazole group and in 16.7% receiving placebo (cryptococcal meningitis (n = 7), *T. marneffei* (n = 4); P = 0.003)).

Chromoblastomycosis

Two prospective, uncontrolled studies evaluated the effectiveness of itraconazole in a small number of patients with chromoblastomycosis infection due to *Fonsecaea pedrosoi* (*31, 32*). At a dose of 200–400 mg/day itraconazole, 42% of patients with mild to moderate disease achieved a clinical and biological cure after a mean therapy duration of 7.2 months (3.2–29.6 months). Clinical improvement was observed in 21% of patients with severe lesions after a mean 17.6 months of treatment (10.7–22.5 months). In total, 12 (63%) of 19 patients benefited from itraconazole treatment (*31*). In a small study of 10 patients given 100–200 mg/day itraconazole, 90% of patients showed benefit (cure, major improvement or minor improvement) after 12 months of treatment (*32*).

Itraconazole is included as a recommended (or alternative) treatment for the proposed infections in international guidelines (*33–36*).

Summary of evidence – harms (from the application)

Known adverse events associated with itraconazole include gastrointestinal effects, hepatic dysfunction, QT-interval prolongation, rash, metabolic disturbances and cardiovascular events including hypotension, congestive cardiac failure and peripheral oedema. Dose adjustment may be necessary in the presence of renal impairment, and patients with hepatic impairment or taking other hepatotoxic medicines require careful monitoring (*37*).

Itraconazole is associated with a number of drug–drug interactions occurring via several different mechanisms: medicines that inhibit gastric acid secretion, such as antacids, proton-pump inhibitors and H2-antagonists, all reduce absorption of itraconazole capsules. Itraconazole metabolism is accelerated by concomitant administration of rifampicin, phenytoin and carbamazepine, which may mean that therapeutic serum concentrations cannot be achieved (*38*). In addition, many clinically significant interactions relate to the suppression of CYP3A4 (cytochrome P450 3A4) activity by itraconazole, which leads to higher exposures to agents that are metabolized via this route. Itraconazole also prolongs the action of midazolam, digoxin, ciclosporin, tacrolimus, sirolimus, statins and warfarin (*39–42*). There are also clinically important interactions between itraconazole and many antiretroviral medicines.

Additional evidence (not in the application)

Differences in bioavailability between itraconazole capsules and oral liquid are considerable and the two formulations are not interchangeable. Itraconazole oral liquid has better oral bioavailability than itraconazole capsules and produces approximately 30% higher systemic drug exposure (*43*). Oral bioavailability of itraconazole capsules is affected by the presence of food, which is not the case with itraconazole oral liquid.

WHO guidelines

N/A

Costs/Cost–effectiveness

The mean daily treatment cost for 400 mg itraconazole was estimated at US$ 6.73. Costs were estimated in the application to range from less than US$ 0.01 in Sri Lanka and Zambia to US$ 102 in Sweden.

Availability

Widely available, including generics

Other considerations

The Expert Committee considered that therapeutic drug monitoring (TDM), where available, may help inform management considerations, especially with regard to preventing underdosing. In severe infections, however, the Committee felt that the clinical benefits of unmonitored therapy would often outweigh the benefits of additional TDM and thus considered that core listing (as opposed to Complementary Listing) was appropriate.

Committee recommendations

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.

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Voriconazole – addition – EML and EMLc

Voriconazole — ATC Code: J02AC03

Proposal

The application requested addition of voriconazole to the core list of the EML and EMLc for the treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.

Applicant(s)

Global Action Fund for Fungal Infection, Geneva, Switzerland, in association with the International League of Dermatological Societies, Manchester University, Manchester, England, and the Medical Mycology Reference Laboratory of the Instituto de Salud Carlos III, Madrid, Spain

WHO technical department

N/A

EML/EMLc

EML and EMLc

Section

6.3 Antifungal medicines

Dose form(s) and strength(s)

Tablet: 50 mg; 200 mg

Powder for injection: 200 mg in vial

Powder for oral liquid: 40 mg/mL

Core/Complementary

Core

Individual/Square box listing

Individual

Background (if relevant, e.g. resubmission, previous EC consideration) Voriconazole has not previously been considered for addition to the EML and EMLc.

The current EML and EMLc include fluconazole with a square box as the representative of the pharmacological class of azole antifungals. However, fluconazole has no activity against infections caused by filamentous fungi including chronic pulmonary aspergillosis and invasive aspergillosis.

Public health relevance (burden of disease)

Chronic pulmonary aspergillosis (CPA) is estimated to affect more than 3 million people worldwide, of whom approximately 1.2 million have had tuberculosis (*1*). Following pulmonary tuberculosis, 25–33% of patients are left with residual cavitation in the lung and, of these, 10–35% develop CPA. Five-year survival without antifungal treatment is approximately 20% (*2, 3*).

It is estimated that more than 200 000 people develop acute invasive aspergillosis annually (*4*). The disease is common in people with acute leukaemia, those who have haematopoietic stem cell transplantation (HSCT) and other transplant recipients (*5*). Less commonly, invasive aspergillosis occurs in people receiving corticosteroids for many reasons including chronic obstructive pulmonary disease (>1.2% of admissions to hospital), lung cancer and autoimmune disorders (such as systemic lupus erythematosus) (*6*). Other significant risk factors include medical intensive care, liver failure and severe burns (*7*). However, as some of these conditions are more prevalent than haematological cancer and transplantations, the number of individuals with invasive aspergillosis may be higher than estimated. Mortality without antifungal treatment is 100%.

Summary of evidence – benefits (from the application)

The application summarized the outcomes of prospective studies of voriconazole in chronic and invasive pulmonary aspergillosis.

Chronic pulmonary aspergillosis

The efficacy and safety of voriconazole were evaluated in a prospective, open, multicentre trial of 41 minimally or non-immunocompromised patients with proven CPA (*8*). The primary end-point was global success at 6 months, defined as complete or partial (≥50% improvement) radiological response and mycological eradication. Global success at 6 months was reported in 13/41 (32%) patients (95% confidence interval (CI) 18.1–48.1 %): 10/19 (53%) with chronic necrotizing aspergillosis and 3/22 (14%) with chronic cavitary aspergillosis ($P = 0.01$). The respective success rates at the end of therapy were 58% and 32%.

Acute invasive aspergillosis

Voriconazole and amphotericin B were compared as primary therapy for invasive aspergillosis in 277 treated patients in a randomized, unblinded trial (*9*). Most patients had underlying allogeneic HSCT, acute leukaemia or other haematological diseases.

At week 12, for the modified intention-to-treat population, a complete or partial response to therapy ("successful outcome") was achieved in 52.8% of the patients in the voriconazole group compared with 31.6% of patients in the amphotericin B group (absolute difference 21.2%; 95% CI 10.4–32.9). Survival rates at 12 weeks for voriconazole and amphotericin B were 70.8% and 57.9%, respectively (hazard ratio (HR) 0.59; 95% CI 0.40–0.88). As the lower bound of the 95% CI was above zero, the authors concluded that voriconazole was non-inferior and superior to amphotericin B.

A subsequent study followed the same population and reported the outcomes for patients who switched from voriconazole or amphotericin B to other licensed antifungal therapies (OLAT) (*10*). Of voriconazole-treated patients, 36% switched to OLAT, compared with

80% of amphotericin B treated patients. Switches were made because of intolerance or insufficient response in 24% and 70% of the voriconazole and amphotericin B groups, respectively.

The application also summarized international guideline recommendations for voriconazole in adults and children. The Infectious Diseases Society of America (IDSA) recommends voriconazole for treatment of invasive aspergillosis in adults and children (strong recommendation, high-quality evidence) (*11*). ISDA and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) also recommend voriconazole for treatment of CPA in adults and children (strong recommendation, high-quality evidence) (*11, 12*).

Summary of evidence – harms (from the application)

Known adverse events associated with voriconazole include transient visual disturbances, potentially dose-limiting hepatotoxicity, skin rash, erythroderma, photosensitivity, cheilitis and perioral excoriations, nausea, vomiting, diarrhoea, visual or auditory hallucinations, and cardiovascular events including tachyarrhythmias and QT-interval prolongations on electrocardiography. There have also been rare cases of arrhythmia (including torsade de pointes and bradycardia), cardiac arrest and sudden death in patients taking voriconazole, probably related to excessive plasma concentrations; these cases usually involve patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia, and concomitant medication (e.g. quinolones) that may be contributory.

Reversible central and peripheral neurological symptoms and hallucinations may be observed in association with higher drug concentrations but with significant variability; these may be confused with other etiologies of CNS dysfunction. Voriconazole concentrations may be a predictor of CNS neurotoxicity, which is reversible.

Peripheral neuropathy – usually sensory, sometimes motor or mixed – may occur after months of therapy and may be concentration-dependent.

Prolonged use of voriconazole (e.g. for osteomyelitis or meningitis) for prophylaxis has revealed newer toxicities including periostitis with severe pain in bones or joints and elevated serum fluoride levels. The risk for squamous cell carcinoma or melanoma in sun-exposed areas is increased by concomitant immunosuppression and chronic voriconazole use, especially in fair-skinned individuals (*11*).

Voriconazole is metabolized via cytochrome P450 3A4, 2C9 and 2C19 pathways and is thus associated with a number of drug–drug interactions including (but not limited to) selected antiretroviral medicines, rifampicin, antiepileptic medicines, ciclosporin, statins, opioids, warfarin and prednisolone. Care is required in its prescribing and therapeutic drug monitoring (TDM) is often recommended.

Additional evidence (not in the application)

N/A

WHO guidelines

N/A

Costs/Cost–effectiveness

The application stated that generic voriconazole has recently been introduced and that prices are consequently changing in many countries although they remain generally high. Daily treatment costs for oral voriconazole are estimated to vary from US$ 2.08 in Pakistan to US$ 94.00 in Thailand.

Availability

Widely available

Other considerations

The Expert Committee considered that TDM, where available, may help inform management considerations, especially with regard to preventing underdosing. In severe infections, however, the Committee felt that the clinical benefits of unmonitored therapy would often outweigh the benefits of additional TDM, and thus considered that core listing on the EML (as opposed to Complementary Listing) was appropriate.

Committee recommendations

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.

References

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6.4: Antiviral medicines

6.4.2: Antiretrovirals

ARV formulations - deletion - EML and EMLc

Various antiretroviral medicines/ formulations (deletion) **ATC Code: various**

Proposal

The applications requested deletion of various antiretroviral medicines or formulations from the EML and/or EMLc.

Applicant(s)

Dr Marco Vitoria, WHO Department of HIV/AIDS (various)

F. Hoffmann-La Roche Ltd (saquinavir)

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML and EMLc (as specified in the applications)

Section

6.4.2 Antiretrovirals

Dose form(s) and strength(s)

Various

Core/Complementary

Core

Individual/Square box listing

Individual

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

Follow-up actions from the 2015 Expert Committee

The 2015 Expert Committee recommended deletion from the EML and EMLc in 2017 of the following medicines without further discussion unless an application was received to support their retention (*1*).

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	x
stavudine	Capsule: 15 mg; 20 mg; 30 mg	x	x
	Powder for oral liquid: 5 mg/mL	x	x
zidovudine	Capsule: 100 mg	x	x

WHO's Department of HIV/AIDS continues to support the deletion of these medicines from the EML and EMLc, with the exception of lamivudine oral liquid. 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* (*2*) for the treatment of newborns, and on this basis the applicant requested it be retained on the EMLc.

Public health relevance (burden of disease)

N/A

Summary of evidence – benefits (from the application)

WHO Department of HIV/AIDS 2017 update

The rationale provided in the application for the requested new deletions fell into three categories, described below and summarized in the table:

- Category 1: exclusion of the medicine as a therapeutic option in current guidelines. The medicine is in the current EML/EMLc and is not recommended as a therapeutic option in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.*
- Category 2: exclusion of the formulation as a therapeutic option in current guidelines. Dose in the current EML is not aligned with the recommended dosing in the 2016 WHO Consolidated guidelines.
- Category 3: 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 (*3*).

Medicine	*Dose form/strength/ formulation*	*Delete EML*	*Delete EMLc*	*Deletion category*
atazanavir	Solid oral dose form: 150 mg	x	x	3
lamivudine + nevirapine + stavudine	Tablet: 150 mg + 200 mg + 30 mg	x	N/A	1
	Tablet (dispersible): 30 mg + 50 mg + 6 mg	x	x	1
nevirapine	Tablet: 200 mg	–	x	3
saquinavir	Solid oral dose form: 200 mg; 500 mg (as mesylate)	x	N/A	1
zidovudine	Solution for IV infusion injection: 10 mg/mL in 20-mL vial	x	N/A	2

The application from Roche stated that clinical use of the protease inhibitor saquinavir has declined over time with the introduction of newer antiretroviral agents with lower pill burden, similar or greater effectiveness and lower risk of toxicity. Unlike other protease inhibitors, saquinavir is associated with QT prolongation and a requirement for ECG monitoring. Numerous alternative protease inhibitors (with and without ritonavir) remain listed on the EML.

Summary of evidence – harms (from the application)

N/A

Additional evidence (not in the application)

N/A

WHO guidelines

The proposed deletions are in alignment with recommendations in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* and with the IATT Paediatric ARV Formulary, revised in 2016.

Costs/Cost–effectiveness

N/A

Availability

In consideration of the consequences of the proposed deletions:

- atazanavir: 100 mg remains available on EML and EMLc, 300 mg remains available on

EML; an FDC formulation of atazanavir + ritonavir (300 mg + 100 mg) has been added to the EML in 2017.

- lamivudine + nevirapine + stavudine: deletion will remove all available formulations from the EML/EMLc of this FDC.
- nevirapine: 200-mg tablets remain on the EML; the EMLc includes oral liquid 50 mg/mL and 50-mg dispersible tablets.
- saquinavir: numerous alternative protease inhibitors (with and without ritonavir in FDCs) are available on the EML.
- zidovudine: currently the only HIV medicine on the EML that comes in a parenteral dose form; multiple alternative oral dose forms of zidovudine are available, including in FDCs.

Other considerations

With the exception of the request from the WHO Department of HIV/AIDS to retain lamivudine oral liquid on the EMLc, no applications were received to support retention of any of the medicines flagged for deletion in 2015.

Committee recommendations

Recalling the recommendation from the 2015 meeting, the Expert Committee recommended the deletion from the EML and EMLc of abacavir oral liquid 100 mg/5 mL, efavirenz capsules 50 mg, 100 mg and 200 mg, stavudine capsules 15 mg, 20 mg and 30 mg and powder for oral liquid 5 mg/mL, and zidovudine capsules 100 mg. Noting the advice from the WHO Department of HIV/AIDS about the continued recommendation in current WHO guidelines for use of lamivudine oral liquid for the treatment of newborns, the Expert Committee recommended that it be deleted from the EML but retained on the EMLc.

The Committee considered the rationale behind the new proposals to delete atazanavir, lamivudine + nevirapine + stavudine, nevirapine and saquinavir formulations to be reasonable and therefore recommended deletion of the items as proposed.

In the case of zidovudine solution for IV infusion injection, the Committee noted that, although not included in current WHO HIV guidelines, it is still recommended by a number of other international guidelines for HIV-positive women who have viral loads greater than 1000 copies/mL and are therefore considered to be at high risk for maternal-to-newborn HIV transmission. The Committee therefore recommended zidovudine solution for IV infusion injection be retained on the EML for the subset of HIV-positive pregnant patients who are at high risk of transmitting the infection to their newborns.

References

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2. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection:

recommendations for a public health approach, second edition. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 19 January 2017).

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6.4.2.1: Nucleoside/Nucleotide reverse transcriptase inhibitors

Abacavir – change: new formulation and strength - EMLc

Abacavir **ATC Code: J05AF06**

Proposal

The application requested addition of a new formulation of abacavir to the core list of the EMLc for the treatment of children with HIV infection.

Applicant(s)

Dr Martina Penazzato, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EMLc

Section

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

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Dose form(s) and strength(s)

Tablet (dispersible, scored): 60 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Abacavir has been included on the EMLc since 2007. Evidence for effectiveness and safety was evaluated at the time of listing.

Abacavir (ABC) oral liquid 100 mg/5 mL is currently the only formulation of abacavir included on the 5th EMLc (2015). It has been proposed for deletion in 2017 in accordance with the 2015 Expert Committee recommendation.

Public health relevance (burden of disease)

There were 150 000 new paediatric HIV infections in 2015, and 1.8 million children are now

living with HIV (*1*). There is evidence that, without antiretroviral treatment (ART), more than 50% of infected infants will progress to AIDS and death by age 2 years (*2*).

Age-appropriate dosage forms for use in infants and children are necessary for the successful scaling-up of treatment for paediatric HIV infection.

Summary of evidence – benefits (from the application)

Evidence for the clinical effectiveness of abacavir was evaluated at the time of listing.

Abacavir 60-mg dispersible, scored tablets are included on the "Limited Use" paediatric ARV formulary list of the Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children for use in children under 3 years of age who are undergoing tuberculosis treatment and require a triple nucleoside ART (*3*).

The application described a review of abacavir use in paediatric patients which found that there was benefit, in terms of increased antiretroviral activity, of a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen containing zidovudine, lamivudine and abacavir compared with zidovudine, lamivudine and placebo (*4*). The application also described findings of the ARROW study: viral load suppression was similar to standard non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART at 48 weeks for children coinfected with TB who moved to a triple-NRTI regimen containing abacavir, and was significantly lower at 144 weeks (*5*).

Advantages of dispersible tablet formulations over syrups include ease of transport and lower transport and production costs; they can be used for very young children and may be dispersed in breast milk or formula. Scored tablets provide flexibility of dosing across age and weight ranges.

Summary of evidence – harms (from the application)

Evidence for the safety of abacavir was evaluated at the time of listing.

Additional evidence (not in the application)

N/A

WHO guidelines

Abacavir is recommended in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* as part of the NRTI backbone for infants and children under 3 years of age (strong recommendation, moderate-quality evidence).

Abacavir is also a recommended option as part of the NRTI backbone for first-line ART in children aged 3–10 years (conditional recommendation, moderate-quality evidence).

It is also recommended as part of triple NRTI treatment for children who develop TB while on an ART regimen containing nevirapine or ritonavir-boosted lopinavir (strong recommendation, moderate-quality evidence) (*6*).

Costs/Cost–effectiveness

The average reported price per patient per year for abacavir dispersible tablets is US$ 95 compared with US$135 for abacavir oral liquid. The application also claimed savings in terms of reduced shipment, storage and wastage costs compared with oral liquid.

Availability

Abacavir 60 mg dispersible tablets are included on the WHO List of Prequalified Medicinal Products. They are produced by Cipla Limited and Micro Labs Limited, India.

Other considerations

N/A

Committee recommendations

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.

References

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Zidovudine (ZDV or AZT) - change: new formulation and strength - EMLc

Zidovudine **ATC Code: J05AF01**

Proposal

The application requested addition of a new formulation of zidovudine to the core list of the EMLc for the treatment of children with HIV infection.

Applicant(s)

Dr Martina Penazzato, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EMLc

Section

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

Dose form(s) and strength(s)

Tablet (dispersible, scored): 60 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Zidovudine has been included on the EMLc since 2007. Evidence for effectiveness and safety was evaluated at the time of listing.

Zidovudine capsules 100 mg and oral liquid 50 mg/mL are currently included on the 5th EMLc (2015). Zidovudine capsules have been recommended for deletion in 2017 in accordance with the 2015 Expert Committee recommendation.

Public health relevance (burden of disease)

In 2015 there were 150 000 new paediatric HIV infections, and 1.8 million children are now living with HIV (*1*). There is evidence that, without antiretroviral treatment (ART), more

than 50% of infected infants will progress to AIDS and death by age 2 years (*2*).

Age-appropriate dosage forms for use in infants and children are necessary for the successful scaling-up of treatment for paediatric HIV infection.

Summary of evidence – benefits (from the application)

Evidence for the clinical effectiveness of zidovudine was evaluated at the time of listing.

Zidovudine 60 mg dispersible, scored tablets are included on the "Limited Use" paediatric ARV formulary list by the Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children for use in children under 3 years of age who are undergoing tuberculosis treatment and require a triple nucleoside ART regimen (*3*).

The application described findings of the ARROW study, a randomized paediatric trial in Ugandan children comparing clinical and laboratory monitoring of three ART regimens, which also reported the incidence of TB diagnosis in the study population. The investigators found that viral load suppression was similar to standard non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART at 48 weeks for children coinfected with TB who moved to a triple-NRTI regimen containing zidovudine, and significantly lower at 144 weeks (*4*).

Advantages of dispersible tablet formulations over syrups include ease of transport and lower transport and production costs; they can be used for very young children and may be dispersed in breast milk or formula. Scored tablets provide for flexibility of dosing across age and weight ranges.

Summary of evidence – harms (from the application)

Evidence for the safety of zidovudine was evaluated at the time of listing.

Additional evidence (not in the application)

N/A

WHO guidelines

Zidovudine is recommended in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* as part of the NRTI backbone for infants and children under 3 years of age (strong recommendation, moderate-quality evidence).

Zidovudine is also a recommended option as part of the NRTI backbone for first-line ART in children aged 3–10 years (conditional recommendation, moderate-quality evidence).

It is also recommended as part of triple NRTI treatment for children who develop TB while on an ART regimen containing nevirapine or ritonavir-boosted lopinavir (strong recommendation, moderate-quality evidence) (*5*).

Costs/Cost–effectiveness

The average reported price per patient per year for zidovudine dispersible tablets is US$ 40 compared with US$ 89 for zidovudine oral liquid. The application also claimed savings in terms of reduced shipment, storage and wastage costs compared with oral liquid.

Availability

Zidovudine 60 mg dispersible tablets are included on the WHO List of Prequalified Medicinal Products. They are produced by Sun Pharmaceutical Industries Limited, India.

Other considerations

Weight restriction >3 kg

Committee recommendations

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.

References

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6.4.2.3: Protease inhibitors

Atazanavir + ritonavir – addition – EML

Atazanavir + ritonavir **ATC Code: to be assigned**

Proposal

The application requested addition of a fixed-dose combination tablet of atazanavir + ritonavir (ATV/r) to the core list of the EML for the treatment of HIV infection in adults and adolescents.

Applicant(s)

Dr Marco Vitoria, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML

Section

6.4.2.3 Protease inhibitors

Dose form(s) and strength(s)

Tablet (heat-stable): 300 mg (as sulfate) + 100 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Atazanavir 300-mg tablets and ritonavir 10-mg tablets are both currently included individually on the EML.

Public health relevance (burden of disease)

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were in low- and middle- income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving antiretroviral therapy in 2015 (*1*).

Summary of evidence – benefits (from the application)

Evidence for the clinical effectiveness of atazanavir and ritonavir was evaluated at the time of their individual listings.

The application described a recent retrospective study in Nigeria that evaluated virological and immunological outcomes in patients switched from ritonavir-boosted lopinavir (LPV/r) to an ATV/r-based second-line treatment regimen (2). This study found improvements in immunological responses and no increased risk of virological failure in patients switched from LPV/r- to ATV/r-containing regimens after 24 months of follow-up.

Summary of evidence – harms (from the application)

Evidence for the safety of atazanavir and ritonavir was evaluated at the time of their individual listings.

The application described the most common adverse events associated with atazanavir and ritonavir, warnings and precautions, drug interactions and precautions for special populations, with reference to the USA product labels of the two component products.

Additional evidence (not in the application)

Another recent prospective study in high income countries (HIV-CAUSAL Collaboration, 2004–2013) (*3*) has shown significantly lower mortality, lower incidence of AIDS-defining illness, a greater 12-month increase in CD4 cell count, and a smaller risk of virological failure at 12 months for ritonavir-boosted atazanavir compared with ritonavir-boosted lopinavir. The hazard ratios (HR) for ATZ/r versus LPV/r were significantly lower: HR 0.70 (95% confidence interval (CI) 0.53–0.91) for death; HR 0.67 (95% CI 0.55–0.82) for AIDS-defining illness or death; and HR 0.91 (95% CI 0.84–0.99) for virological failure at 12 months. The mean 12-month increase in CD4 count was 8.15 (95% CI –0.13 to 16.43) cells/mm3 (higher in the ATZ/r group).

WHO guidelines

ATV/r is recommended in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* as one of the preferred protease inhibitors (with LPV/r) for second-line treatment of adults, adolescents and pregnant or breastfeeding women, in combination with an appropriate nucleoside reverse-transcriptase inhibitor (NRTI) backbone (*4*).

A comparative analysis of the characteristics of available ritonavir-boosted protease inhibitors is presented in the guidelines. The advantages of ATV/r compared with LPV/r include the lower pill burden with once daily dosing, and better gastrointestinal tolerability; disadvantages include the incidence of hyperbilirubinaemia and dyslipidaemia and contraindication for patients on rifampicin-containing antituberculosis regimens.

Costs/Cost–effectiveness

The average reported price per patient per year for ATV/r FDC 300 mg/100 mg tablets is US$ 203, compared with US$ 251 for the component medicines supplied separately. The

application also claims cost savings associated with the need for fewer packs, and the advantage of simplifying country supply chain management with consolidation around a single FDC product.

Availability

ATV/r 300-mg (as sulfate)/100-mg tablets are included on WHO's List of Prequalified Medicinal Products. They are produced by Mylan Laboratories Limited, and Cipla Limited, India.

Other considerations

N/A

Committee recommendations

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.

References

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Lopinavir + ritonavir - change: new formulation and strength - EMLc

Lopinavir + ritonavir — ATC Code: J05AR10

Proposal

The application requested addition of a new formulation of lopinavir + ritonavir fixed-dose combination to the core list of the EMLc for the treatment of children with HIV infection.

Applicant(s)

Dr Martina Penazzato, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EMLc

Section

6.4.2.3 Protease inhibitors

Dose form(s) and strength(s)

Capsule (containing oral pellets): 40 mg + 10 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Fixed-dose combinations of lopinavir + ritonavir (LPV/r) have been included on the EMLc since 2007. Currently listed formulations are oral liquid (400 mg + 100 mg/5 mL) and heat-stable tablets (100 mg + 25 mg).

Public health relevance (burden of disease)

In 2015 there were 150 000 new paediatric HIV infections, and 1.8 million children are now living with HIV (*1*). There is evidence that, without antiretroviral treatment (ART), more than 50% of infected infants will progress to AIDS and death by age 2 years (*2*).

Age-appropriate dosage forms for use in infants and children are necessary for the successful scaling-up of treatment for paediatric HIV infection.

Summary of evidence – benefits (from the application)

Evidence for the clinical effectiveness of LPV/r in paediatric patients was evaluated at the time of listing.

The application provided brief summaries of the results of two randomized controlled trials (*3, 4*) on the basis of which the decision was made to recommend LPV/r as first-line antiretroviral treatment for children under the age of 3 years in the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*5*).

The application also described the CHAPAS-2 study – an open-label, randomized, comparative bioavailability trial of LPV/r liquid, pellet and tablet formulations in HIV-infected infants and children (*6, 7*). In the cohorts of patients aged 3–12 months and 1–<4 years, LPV concentrations and pharmacokinetic parameters were slightly higher with pellets than with liquid formulation. For the cohort of older patients (4–<13 years), LPV concentrations were higher with paediatric tablets than with pellets. For patients under 4 years of age, LPV/r pellets were rated by caregivers as being more acceptable than oral solution.

In 2016, LPV/r pellets were added to the Optimal List of the Interagency Task Team (IATT) Paediatric ARV Formulary (*8*). In making this recommendation, the IATT considered that, in resource-limited settings, the LPV/r pellet formulation can offer advantages over LPV/r oral liquid (which is not heat-stable and requires cold-chain transport).

Summary of evidence – harms (from the application)

Evidence for the safety of LPV/r in paediatric patients was evaluated at the time of listing.

The application described the most common adverse events, warnings and precautions, and drug interactions associated with LPV/r, with reference to the USA product label.

Additional evidence (not in the application)

N/A

WHO guidelines

The 2016 WHO C*onsolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* make the following recommendations in relation to LPV/r:

- An LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than 3 years (36 months) of age, regardless of NNRTI (non-nucleoside reverse transcriptase inhibitor) exposure. If LPV/r is not feasible, treatment should be initiated with a nevirapine-based regimen (strong recommendation, moderate-quality evidence).
- After failure of a first-line NNRTI-based regimen, children should be switched to a boosted protease inhibitor-based regimen. LPV/r or ATV/r is preferred (conditional recommendation, very low-quality evidence) (*9*).

Costs/Cost–effectiveness

The average reported price per patient per year for LPV/r pellets is US$ 467, compared with US$ 150 and US$ 100 for the oral solution and tablets, respectively. The application stated that, although more expensive, the pellets represent an alternative for fulfilling the recommendation of LPV/r as first-line treatment for all patients under 3 years of age in low-resource settings that may lack a heat-stable, child-friendly formulation.

The application described cost savings associated with freight and storage compared with the oral solution.

Availability

This formulation is produced by Cipla Ltd, India

Other considerations

N/A

Committee recommendations

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.

References

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6.4.2.4: Integrase inhibitors – new subsection

Dolutegravir – addition – EML

Dolutegravir **ATC code: J05ZA12**

Proposal

The application requested addition of dolutegravir to the core list of the EML for the treatment of HIV-1 infection in adults and adolescents as an alternative first-line treatment, or as a second-line treatment option in patients failing other non-nucleoside reverse transcriptase- or protease inhibitor-based regimens.

Applicant(s)

Dr Marco Vitoria, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML

Section

New subsection: 6.4.2.4 Integrase inhibitors

Dose form(s) and strength(s)

Tablet: 50 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Single-agent integrase strand transfer inhibitors (INSTIs or integrase inhibitors) had not previously been considered by the Expert Committee. A separate application to this meeting requested the addition of an alternative integrase inhibitor, raltegravir, for second-line treatment.

Public health relevance (burden of disease)

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95%

were in low- and middle- income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving antiretroviral therapy in 2015 (*1*).

Summary of evidence – benefits (from the application)

The application presented the results of three randomized controlled phase III studies in support of the efficacy of dolutegravir in ART-naive patients.

The SPRING-2 non-inferiority study compared dolutegravir and raltegravir over 96 weeks, regardless of baseline viral load and nucleoside reverse-transcriptase inhibitor (NRTI) backbone (*2*). At 96 weeks, dolutegravir was found to be non-inferior to raltegravir, with 81% of patients in the dolutegravir group having HIV-RNA <50 copies/mL compared with 76% in the raltegravir group (adjusted mean difference 4.5%; 95% confidence interval (CI) –1.1% to 10%).

The SINGLE study compared dolutegravir in combination with abacavir + lamivudine with emtricitabine + efavirenz + tenofovir disoproxil fumarate in 833 participants who had not received previous treatment for HIV infection (*3*). The dolutegravir combination met the criterion for superiority, with a greater proportion of patients achieving an HIV-RNA level of <50 copies/mL at 48 weeks (88% versus 81%; adjusted treatment difference 7%; 95% CI 2–12%). The dolutegravir group also had more favourable outcomes for the secondary end-points of time to viral suppression, changes in CD4+ T-cell count from baseline, safety and antiviral resistance.

The FLAMINGO study compared dolutegravir with ritonavir-boosted darunavir, each in combination with two NRTIs (*4*). At 96 weeks, a statistically significantly greater proportion of the dolutegravir group had HIV-1 RNA <50 copies/mL (adjusted mean difference 12.4%; 95% CI 4.7–20.2%; $P = 0.002$).

The application also presented the results of two phase III studies of dolutegravir in treatment-experienced adult patients.

The SAILING study compared dolutegravir and raltegravir (with background therapy). The proportion of patients with treatment-emergent integrase-inhibitor resistance was a prespecified secondary end-point. At 48 weeks, the proportion of patients in each group with HIV-1 RNA <50 copies/mL was 71% for dolutegravir versus 64% for raltegravir (adjusted mean difference 7.4%; 95% CI 0.7–14.2%), and superiority was concluded. In addition, significantly fewer patients in the dolutegravir group had virological failure due to treatment-emergent resistance (4 versus 17 patients; adjusted difference –3.7; 95% CI –6.1 to –1.2) (*5*).

In the VIKING-3 single-arm study, twice daily dolutegravir in combination with other antiretroviral therapy (ART) was shown to be effective in ART-experienced patients demonstrating integrase inhibitor resistance: 69% of patients with prior virological failure and resistance to other integrase inhibitors achieved virological suppression at week 24 (*6*).

The IMPAACT P1093 clinical trial of dolutegravir plus two NRTIs in treatment-experienced individuals assessed the pharmacokinetics and efficacy of dolutegravir in treatment-experienced adolescents. In the age cohort 12–18 years, 70% and 61% of patients had HIV-

RNA <50 copies/mL at weeks 24 and 48, respectively (*7*).

Summary of evidence – harms (from the application)

The safety profile of dolutegravir compared favourably with that of other antiretrovirals in the above-mentioned clinical trials. The most common clinical adverse effects in the SPRING-2 and SINGLE studies were nausea, nasopharyngitis, diarrhoea and headache. The occurrence of adverse events leading to treatment discontinuation was low and comparable across treatment groups (*2, 3*).

Dolutegravir has also been associated with hepatotoxicity and hypersensitivity reactions (*8*).

Additional evidence (not in the application)

N/A

WHO guidelines

Dolutegravir 50 mg is included in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* as an alternative first-line treatment option in combination with a dual NRTI backbone for adults and adolescents (*8*).

A systematic review and network meta-analysis of 71 trials involving 34 032 patients was conducted to inform the WHO guidelines and assessed the comparative evidence on the efficacy and safety of INSTIs (dolutegravir, raltegravir and elvitegravir + cobicistat) and efavirenz in adult patients with HIV. The review found moderate-quality evidence that two NRTIs + INSTI was a generally more effective regimen than two NRTIs plus efavirenz 600 mg. Dolutegravir and raltegravir had comparable effect, but were better than elvitegravir + cobicistat in terms of viral suppression and treatment discontinuation.

Compared with efavirenz 600 mg, dolutegravir offers advantages that include lower potential for drug interactions, shorter median time to viral suppression and higher genetic resistance barrier.

The WHO guidelines note the limited availability of data regarding the safety and efficacy of dolutegravir in pregnant women and patients coinfected with tuberculosis.

Costs/Cost–effectiveness

The unit price for dolutegravir 50 mg averages US$ 0.127 compared with US$ 0.111 for efavirenz 600 mg. The application claimed that, with increasing volumes and generic manufacture, the unit price of dolutegravir is expected to decline, and pricing agreements will be refined.

Availability

Dolutegravir is available from ViiV Healthcare, United Kingdom; Aurabindo Pharma Limited, India.

Generic versions of dolutegravir 50 mg received tentative approval from the U.S. Food &

Drug Administration in August 2016. Dolutegravir 50 mg is also included on WHO List of Prequalified Medicinal Products.

Other considerations

Weight restriction of >40 kg

Medicines Patent Pool (MPP): GSK have signed an agreement for dolutegravir with MPP.

Committee recommendations

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.

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Raltegravir – addition – EML and EMLc

Raltegravir **ATC Code: J05AX08**

Proposal

The application requested addition of raltegravir to the core list of the EML and EMLc for the treatment of HIV-1 infection as an alternative regimen for second- or later-line treatment in adults, and for second-line treatment of paediatric patients who have failed a protease inhibitor-based regimen.

Applicant(s)

Dr Marco Vitoria, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML and EMLc

Section

New subsection: 6.4.2.4 Integrase inhibitors

Dose form(s) and strength(s)

Tablet: 400 mg

Tablet (scored): 100 mg

Tablet (chewable): 25 mg

Core/Complementary

Core

Individual/Square box listing

Individual

Background (if relevant, e.g. previous EC consideration)

Single-agent integrase inhibitors had not previously been considered by the Expert Committee. A separate application to this meeting requested the addition of an different integrase inhibitor, dolutegravir, as an alternative first-line treatment.

Public health relevance (burden of disease)

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were in low- and middle- income countries. There were 2.1 million new HIV-1

infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving antiretroviral therapy in 2015 (*1*).

There were 150 000 new paediatric HIV infections in 2015, and 1.8 million children are now living with HIV (*1*). There is evidence that, without antiretroviral treatment (ART), more than 50% of infected infants will progress to AIDS and death by age 2 years (*2*).

Summary of evidence – benefits (from the application)

The application presented the findings of several studies.

Pooled results of the BENCHMRK-1 AND BENCHMRK-2 double-blind, randomized, phase III studies of raltegravir in combination with optimized background therapy (OBT) versus OBT alone in patients with HIV who have documented triple-class resistance showed that, at week 96, 55% of the raltegravir group had achieved virological suppression (HIV-RNA <50 copies/mL) compared with 27% of the OBT group. The raltegravir group also had greater mean change in CD4 count from baseline than controls (118 cells/mm3 versus 47 cells/mm3) (*3*).

In the SECOND-LINE study, non-inferiority of raltegravir plus ritonavir-boosted lopinavir (LPV/r) to a regimen of 2–3 nucleoside reverse transcriptase inhibitors (NRTIs) plus LPV/r was demonstrated in adult patients who had failed a standard non-nucleoside reverse transcriptase inhibitor (NNRTI) plus NRTI first-line regimen and who had no prior exposure to integrase inhibitors or protease inhibitors. At 96 weeks, 80% of patients in the raltegravir arm had HIV-RNA levels of <200 copies/mL compared with 76% of control patients. CD4 counts increased from baseline to week 96 in both arms, but there was no statistically significant difference (*4*).

In the EARNEST study, the primary composite end-point of "good disease control" (defined as no new WHO stage 4 events (other than oesophageal candidiasis or mucosal herpes simplex virus infection) or death, a CD4+ count of >250 cells/mm3, and a viral load <10 000 copies/mL at week 96) was achieved by 64% and 60% of patients in the raltegravir group and NRTI groups, respectively. There was no difference between groups in the proportions of patients who had viral suppression <400 copies/mL at 96 weeks (86%) (*5*).

IMPAACT P1006 was a phase I/II open-label, multicentre trial that evaluated the pharmacokinetics, safety, tolerability and efficacy of raltegravir in HIV-infected children aged 2–18 years. Among patients who received the final recommended dose, 53.7% achieved HIV-RNA <50 copies/mL at week 24, and 57.1% had HIV-RNA <50 copies/mL at week 48. Mean increases from baseline in CD4 count were 119 cells/mm3 and 155.7 cells/mm3 at 24 weeks and 48 weeks respectively. Results were consistent across the different age cohorts investigated (*6*).

Summary of evidence – harms (from the application)

Raltegravir was well tolerated in the BENCHMRK trials, with adverse event profiles and laboratory abnormalities generally comparable across the treatment groups. The most common drug-related adverse events were reported as headache, nausea, fatigue and diarrhoea. The rates of development of new, recurrent or progressive cancers were similar across treatment groups (*3*).

Elevations in creatine kinase, together with associated rhabdomyolysis and myopathy, have been observed with raltegravir. Risk is increased by concomitant administration of other medicines known to increase the risk of these events (*7*).

There have been rare reports of severe, life-threatening and fatal skin reactions with raltegravir, including Stevens–Johnson syndrome and toxic epidermal necrolysis.

Additional evidence (not in the application)

WHO guidelines recommend that ART should be initiated in all pregnant and breastfeeding women with HIV, regardless of clinical stage and CD4 cell count. There are limited data on the safety of integrase inhibitors during pregnancy and breastfeeding (*7*). However, raltegravir has been reported to be well tolerated and effective in rapidly reducing viral load in HIV-infected pregnant women presenting late in pregnancy (>32 weeks gestation) and may reduce the risk of mother-to-child transmission (*8–11*).

WHO guidelines

The 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*7*) makes the following recommendations in relation to raltegravir:

- Raltegravir, in combination with LPV/r, is recommended as an alternative second-line treatment option in adults and adolescents (conditional recommendation, low-quality evidence).
- Raltegravir, in combination with dual-NRTI therapy, is the recommended second-line regimen in children younger than 3 years of age who have failed a first-line LPV/r-based regimen (conditional recommendation, very low-quality evidence).
- Raltegravir, in combination with dual NRTI therapy, is a recommended second-line treatment option for children older than 3 years of age who have failed a first-line LPV/r-based regimen (conditional recommendation, very low-quality evidence).

Costs/Cost–effectiveness

The average prices per patient per year for raltegravir are reported as US$ 642 (400 mg), US$ 426 (100 mg) and US$ 657 (25 mg), which are significantly higher than the prices of NRTI and PI alternatives.

Availability

Raltegravir is available from: Merck Sharp & Dohme Ltd, United Kingdom (all strengths); Hetero Lab Ltd, India (400-mg tablets).

Other considerations

N/A

Committee recommendations

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.

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FIXED-DOSE COMBINATIONS

Abacavir + lamivudine – change: new strength – EMLc

Abacavir + lamivudine **ATC Code: J05AR02**

Proposal

The application requested addition of a new strength formulation of abacavir + lamivudine fixed-dose combination tablets to the core list of the EMLc for the treatment of children with HIV infection.

Applicant(s)

Dr Martina Penazzato, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EMLc

Section

6.4.2 Antiretrovirals – fixed-dose combinations

Dose form(s) and strength(s)

Tablet (dispersible, scored): 120 mg (as sulfate) + 60 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

A different strength formulation of abacavir + lamivudine fixed-dose combination (FDC) dispersible scored tablet (60 mg + 30 mg) was added to the EML and EMLc in 2015.

Individually, abacavir and lamivudine have been included on the EMLc since 2002.

Public health relevance (burden of disease)

There were 150 000 new paediatric HIV infections in 2015, and 1.8 million children are now living with HIV (*1*). There is evidence that, without antiretroviral treatment (ART), more than 50% of infected infants will progress to AIDS and death by age 2 years (*2*).

Age-appropriate dosage forms for use in infants and children are necessary for the successful scaling-up treatment of paediatric HIV infection.

Summary of evidence – benefits (from the application)

Evidence for the clinical effectiveness of abacavir and lamivudine was evaluated at the time of their listing.

Summary of evidence – harms (from the application)

Evidence for the safety of abacavir and lamivudine was evaluated at the time of their listing.

Additional evidence (not in the application)

N/A

WHO guidelines

The 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*3*) makes the following recommendations in relation to abacavir plus lamivudine:

- Abacavir + lamivudine is one of two recommended nucleoside reverse transcriptase inhibitor (NRTI) backbone first-line ART regimens for infants and children under 3 years of age (strong recommendation, moderate-quality evidence).
- Abacavir + lamivudine + zidovudine is a recommended first-line treatment option for infants and children under 3 years of age who develop tuberculosis while on an ART regimen containing nevirapine or ritonavir-boosted lopinavir (strong recommendation, moderate-quality evidence).
- Abacavir + lamivudine is the preferred first-line NRTI backbone for treatment of children 3–10 years of age (conditional recommendation, moderate-quality evidence).

Costs/Cost–effectiveness

The average reported price per patient per year for abacavir + lamivudine 120 mg + 60 mg dispersible tablets is US$ 85, compared with US$ 100 for the 60 mg + 30 mg tablets and US$ 172 for oral liquid formulations of abacavir and lamivudine. The application also claimed savings in terms of reduced shipment, storage and wastage costs.

Availability

Abacavir + lamivudine 120 mg + 60 mg dispersible tablets are included on WHO List of Prequalified Medicinal Products and are available from Mylan Laboratories Ltd, India.

Other considerations

N/A

Committee recommendations

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.

References

1. AIDS by the numbers – AIDS is not over, but it can be. Geneva: Joint United Nations Programme on HIV/AIDS; 2016 (http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers, accessed 10 January 2017).
2. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236-–3.
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Cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide – rejection – EML

Cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide — ATC Code: J05AR18

Proposal

The application requested addition of a fixed-dose combination formulation of cobicistat (COBI), elvitegravir (EVG), emtricitabine (FTC) and tenofovir alafenamide (TAF) to the core list of the EML for treatment of HIV infection in antiretroviral treatment (ART)-naive adults and children aged 12 years and above. It was also proposed as replacement ART in patients with viral suppression (HIV1-RNA less than 50 copies/mL) on a stable ART regimen.

Applicant(s)

Gilead Sciences Inc., California, USA

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML

Section

6.4.2 Antiretrovirals – fixed-dose combinations

Dose form(s) and strength(s)

Tablet: 150 mg + 150 mg + 200 mg + 10 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

This was the first application seeking listing of COBI + EVG + FTC + TAF fixed-dose combination (FDC) for treatment of HIV infection. The component medicines are not currently included individually on the EML.

In 2015, the Expert Committee considered an application for the listing of a similar FDC formulation, incorporating tenofovir disoproxil fumarate (TDF). The Expert Committee considered that the COBI + EVG + FTC + TDF combination showed non-inferiority in terms

of efficacy and safety compared with TDF + FTC (or lamivudine, 3TC) + efavirenz (EFV), which was the recommended first-line treatment regimen in the 2013 WHO guidelines for treatment of HIV. The Expert Committee acknowledged the advantages offered by an FDC formulation in terms of reducing pill burden and potentially improving adherence, but noted that this FDC had not shown any clinical advantage in terms of efficacy and/or safety over the currently recommended first-line regimens. The Committee noted that the proposed formulation included medicines that are not currently recommended in the WHO guidelines as first-line HIV treatment options and that there was insufficient evidence of a relevant clinical advantage over currently recommended first-line treatments already on the EML. Listing was not recommended (*1*).

Public health relevance (burden of disease)

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were living in low- and middle-income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving ART in 2015 (*2*).

Summary of evidence – benefits (from the application)

The application presented a summary of evidence from two randomized, double-blind clinical trials comparing COBI + EVG + FTC + TAF with COBI + EVG + FTC + TDF in 1733 treatment-naive adults with HIV-1 infection. The pooled results of these trials formed the basis for regulatory approval in Europe and USA. The primary efficacy end-point in both studies was the proportion of subjects with viral load <50 copies/mL at week 48. The TAF combination was found to be non-inferior to the TDF combination for the primary outcome (92% versus 90%; adjusted treatment difference 2.0%; 95% confidence interval (CI) –0.7% to 4.7%) (*3*). At 96 weeks, the proportions with viral load <50 copies/mL were 86.6% and 85.2% in the TAF and TDF arms, respectively (difference 1.5%; 95% CI –1.8% to 4.8%) (*4*).

Evidence was also presented from two studies involving 100 patients, in support of use of the TAF combination in treatment-naive patients aged 12–18 years and weighing at least 35 kg (*5, 6*). Results were consistent with the findings in adults.

The application also presented data from three switching studies in which virologically supressed patients were switched from TDF-based regimens to TAF combination regimens (*7–9*). Viral suppression at week 48 was observed in 97% and 93% of TAF-based and TDF-based treatment arms, respectively (adjusted difference 4.1%; 95% CI 1.6–6.7) (*7*). Switching to a TAF-based regimen was not observed to be associated with significant changes in estimated creatinine clearance, while significant improvements were observed in proteinuria, albuminuria and bone mineral density (*8*). In patients with prior ART failure, a simplified 2-tablet regimen using the TAF FDC plus darunavir was found to be non-inferior to a baseline 5-tablet regimen in terms of durable maintenance of viral suppression (*9*).

Summary of evidence – harms (from the application)

Renal effects: Compared with the TDF combination, the TAF combination was found to be associated with smaller mean serum creatinine increases (0.08 versus 0.12 mg/dL; *P*

< 0.0001), and less proteinuria (median % change –3 versus 20; $P < 0.001$) at 48 weeks (*3*). The positive effects of the TAF combination on renal function were maintained at 96 weeks (*4*). Improvements in renal tubular biomarkers were greater in adolescents given the TAF combination than in those given the TDF combination (*5, 6*), and in patients switching from a TDF-containing regimen (*7–9*).

Bone effects: Compared with the TDF combination, the TAF combination was associated with a smaller decrease in bone mineral density (BMD) at lumbar spine (mean % change –1.30 versus –2.86; $P < 0.0001$) and hip (mean % change –0.66 versus –2.95; $P < 0.0001$) at 48 weeks (*3*). The effect with the TAF combination on lumbar spine BMD was greater after 96 weeks of treatment (mean % change –0.96% versus –2.79; $P < 0.001$) (*4*). In adolescent patients, median % change in spine BMD increased in patients in the TAF arm, while it decreased in patients in the TDF arm (1.25% versus –0.99%; $P < 0.009$) (*5, 6*). Patients switched from TDF-containing regimens to TAF-containing regimens also showed improvements in spine and hip BMD (*7, 8*).

The Expert Committee considered that the measured benefits of the TAF-combination in terms of renal function and bone effects are based on surrogate measures and, with the relatively short-term follow-up (48 weeks), that these may not translate in the longer term into benefits of the same magnitude in more patient-relevant clinical outcomes such as reduced risk of renal failure or fractures.

Additional evidence (not in the application)

No comparison was made in the application of the TAF-combination versus current recommended first-line ART. Current WHO guidelines recommend TDF + 3TC/FTC + EFV as the preferred first-line therapy (strong recommendation, moderate-quality evidence) (*10*). The application for inclusion on the EML of COBI + EVG + FTC + TDF in 2015 presented such a comparison, and non-inferiority was demonstrated. The Expert Committee considered that, while it is likely that the TAF combination is non-inferior, no clinical efficacy advantage of COBI + EVG + FTC + TDF over the current recommended first-line regimens was demonstrated.

WHO guidelines

WHO's 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*10*) make the following recommendations for first-line ART in adults:

- First-line ART for adults should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI).
- TDF + 3TC (or FTC) + EFV as an FDC is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
- If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following alternative options is recommended:
  - AZT + 3TC + EFV

  - AZT + 3TC + NVP
  - TDF + 3TC (or FTC) + NVP

  (conditional recommendation, moderate-quality evidence).

- TDF + 3TC (or FTC) + dolutegravir (DTG) or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternatives to initiate ART (conditional recommendation, moderate-quality evidence).
- Countries should discontinue stavudine (d4T) use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).

Costs/Cost–effectiveness

In USA, wholesale acquisition costs of the TAF combination described in the application was US$ 2577.66 for 30 days' supply (30 tablets).

The application stated that developing countries classified as low- or lower-middle-income by the World Bank, and countries with unmet HIV/AIDS disease burden, are designated as "access countries" which are charged only for production and related costs. It also stated that the price for a 30-day supply of the TAF-combination (to access countries) was US$ 17 (US$ 204 per year).

By way of comparison, the WHO Global Price Reporting Mechanism reports the median treatment cost per year in 2016 for the current preferred first-line ART (TDF + FTC + EFV) as US$ 77.12.

Availability

This product is currently licensed in Australia, Canada, Europe and USA.

Gilead has licensing agreements with generic drug manufacturers in China, India and South Africa, as well as the Medicines Patent Pool, allowing production and sale of generic versions of Gilead HIV medicines in 112 developing countries.

Other considerations

N/A

Committee recommendations

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.

References

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10. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, second edition. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 7 February 2017).

Efavirenz + lamivudine + tenofovir disoproxil fumarate – addition – EML

Efavirenz + lamivudine + tenofovir disoproxil fumarate — ATC Code: J05AR11

Proposal

The application requested addition of a fixed-dose combination formulation of efavirenz + lamivudine + tenofovir disoproxil fumarate (TDF) to the core list of the EML for the treatment of HIV infection in adults and adolescents.

Applicant(s)

Dr Marco Vitoria, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML

Section

6.4.2 Antiretrovirals – fixed-dose combinations

Dose form(s) and strength(s)

Tablet: 400 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)

Core/Complementary

Core

Individual/Square box listing

Individual

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

The EML currently lists a fixed-dose combination (FDC) formulation of efavirenz (EFV) 600 mg + emtricitabine 200 mg + TDF 300 mg, with annotation that emtricitabine is an acceptable alternative to lamivudine, based on knowledge of pharmacology, resistance patterns and clinical trials of antiretrovirals. The intent of this listing should be interpreted to capture formulations comprising efavirenz 600 mg, lamivudine 300 mg and TDF 300 mg. In effect, the application sought listing of a new strength formulation of efavirenz + lamivudine + TDF.

Public health relevance (burden of disease)

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were in low- and middle-income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving antiretroviral therapy (ART) in 2015 (*1*).

Summary of evidence – benefits (from the application)

The ENCORE1 study was a randomized, double-blind, placebo-controlled non-inferiority trial that compared antiretroviral regimens containing EFV 400 mg or 600 mg in combination with emtricitabine and TDF at recommended doses (*2*). At week 96, the proportions of patients with viral load <200 copies/mL were 90.0% and 90.6% in the 400 mg and 600 mg treatment arms, respectively (difference –0.6; 95% confidence interval (CI) –5.2 to 4.0; P = 0.72), supporting non-inferiority.

The Expert Committee recalled the accepted therapeutic equivalence between emtricitabine and lamivudine, as noted in current EML listings, and considered that the findings of the ENCORE1 study could be extrapolated to lamivudine-containing regimens.

Summary of evidence – harms (from the application)

Safety outcomes in ENCORE1 showed that the proportions of patients in each group reporting adverse events were similar. For adverse events related to EFV, the proportions of reported adverse events were 39% in the 400-mg group and 48% in the 600-mg group (difference –8.6; 95% CI –16.4 to –0.9; P = 0.03). The proportions of patients reporting serious adverse events were not statistically significantly different between treatment groups (*2*).

Additional evidence (not in the application)

N/A

WHO guidelines

EFV400 + lamivudine (3TC) (or emtricitabine (FTC)) + TDF is included in the 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* as an alternative first-line treatment option for adults and adolescents (*3*). EFV600 + 3TC (or FTC) + TDF remains the preferred first-line regimen for adults.

A systematic review and network meta-analysis of 71 trials involving 34 032 patients was conducted to inform the WHO guidelines and assessed the comparative evidence of the efficacy and safety of integrase strand transfer inhibitors (INSTI; dolutegravir, raltegravir and elvitegravir + cobicistat) and EFV in adult patients with HIV. The review found moderate-quality evidence of comparable effects in terms of viral load suppression between EFV 400 mg/day and EFV 600 mg/day, and greater effects of EFV 400 mg/day in terms of CD4 cell count recovery. EFV 400 mg/day was protective in terms of treatment discontinuation due to adverse events. There was low-quality evidence of the regimens being comparable with respect to mortality or AIDS-defining illnesses and treatment-emergent serious adverse events.

The WHO guidelines note the limited availability of data regarding the safety and efficacy of EFV 400 in pregnant women and patients coinfected with tuberculosis using rifampicin.

Costs/Cost–effectiveness

The proposed price of EFV400 + 3TC + TDF is US$ 99 per patient per year, which is up to 8% less than the price of EFV600 +3TC + TDF. The price is to be confirmed once the U.S. Food & Drug Administration (FDA) completes the PEPFAR (President's Emergency Plan for AIDS Relief) review in 2017. The average cost of FDCs is higher than that of their components supplied individually. At health-system level, moderate overall cost-savings are claimed in part because the EFV400 combination has fewer treatment-limiting side-effects.

Availability

This FDC is produced by Mylan Laboratories Ltd, India

The product was granted tentative approval by the FDA on 10 March 2017 as part of the PEPFAR drug review programme.

Other considerations

N/A

Committee recommendations

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.

References

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Emtricitabine + tenofovir alafenamide – rejection – EML

Emtricitabine + tenofovir alafenamide ATC Code: J05AR17

Proposal

The application requested addition of a fixed-dose combination formulation of emtricitabine (FTC) and tenofovir alafenamide (TAF) to the core list of the EML for treatment of HIV infection in adults and children aged 12 years and above, in combination with other antiretroviral agents.

Applicant(s)

Gilead Sciences Inc., California, USA

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML

Section

6.4.2 Antiretrovirals – fixed-dose combinations

Dose form(s) and strength(s)

Tablet: 200 mg + 10 mg, 200 mg + 25 mg

The appropriate TAF dosage is governed by the third agent used in the antiretroviral therapy (ART) regimen. TAF 10 mg is indicated for use in regimens involving a boosted protease inhibitor, while TAF 25 mg is indicated for use in regimens involving non-nucleoside reverse transcriptase inhibitors (NNRTIs), unboosted integrase inhibitors (INSTIs) and co-receptor blockers.

Core/Complementary

Core

Individual/Square box listing

Individual

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

This was the first application seeking listing of FTC + TAF for treatment of HIV infection. Neither component medicine is available individually on the EML.

A fixed-dose combination (FDC) of FTC with tenofovir disoproxil fumarate (TDF) has been included on the EML since 2007.

Public health relevance (burden of disease)

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were in low- and middle-income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving ART in 2015 (*1*).

Summary of evidence – benefits (from the application)

For FTC + TAF, results from studies involving cobicistat (COBI) + elvitegravir (EVG) + FTC +TAF were presented (2-4). The findings of these studies are available in the summary for the COBI + EVG + FTC + TAF application.

Bioequivalence has been demonstrated between FTC + TAF 200 mg + 10 mg, administered with COBI + EVG, and FTC + TAF 200 mg + 25 mg administered without a pharmacokinetic enhancer and a single-tablet regimen of COBI + EVG + FTC + TAF (*5*).

Results of switching studies presented in the application suggest the efficacy in terms of maintenance of virological suppression of switching to TAF-containing regimens from TDF-containing regimens (*4, 6–8*), including in patients with renal impairment and multidrug-resistant HIV infection.

Summary of evidence – harms (from the application)

Evidence for harms was taken from the comparison of TAF and TDF in combination with cobicistat, elvitegravir and emtricitabine.

Renal effects: Compared with the TDF combination, the TAF combination was found to be associated with smaller mean serum creatinine increases (0.08 versus 0.12 mg/dL; $P < 0.0001$), and less proteinuria (median % change –3 versus 20; $P < 0.001$) at 48 weeks (*2*). The positive effects of the TAF combination on renal function were maintained at 96 weeks (*9*). Improvements in renal tubular biomarkers were greater in adolescents given the TAF combination than in those given the TDF combination (*3, 10*), and in patients switching from a TDF-containing regimen (*4, 6, 8*).

Bone effects: Compared with the TDF combination, the TAF combination was associated with a smaller decrease in bone mineral density (BMD) at lumbar spine (mean % change –1.30 versus –2.86; $P < 0.0001$) and hip (mean % change –0.66 versus –2.95; $P < 0.0001$) at 48 weeks (*2*). The effect with the TAF combination on lumbar spine BMD was greater after 96 weeks of treatment (mean % change –0.96% versus –2.79; $P < 0.001$) (9). In adolescent patients, median % change in spine BMD increased in patients in the TAF arm, while it decreased in patients in the TDF arm (1.25% versus –0.99%; $P < 0.009$) (*3, 10*). Patients switched from TDF-containing regimens to TAF-containing regimens also showed improvements in spine and hip BMD (*4, 6*).

The Expert Committee considered that the measured benefits of the TAF-combination in terms of renal function and bone effects are based on surrogate measures and, with the relatively short-term follow-up (48 weeks), that these may not translate in the longer term into benefits of the same magnitude in more patient-relevant clinical outcomes such as reduced risk of renal failure or fractures.

Additional evidence (not in the application)

N/A

WHO guidelines

WHO's 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*11*) make the following recommendations for first-line ART in adults:

- First-line ART for adults should consist of two nucleoside reverse transcriptase inhibitors plus an NNRTI or an INSTI.
- TDF + lamivudine (3TC) (or emtricitabine (FTC)) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
- If TDF + 3TC (or FTC) + EFV is contraindicated or unavailable, one of the following alternative options is recommended:
  - AZT + 3TC + EFV
  - AZT + 3TC + NVP
  - TDF + 3TC (or FTC) + NVP

  (conditional recommendation, moderate-quality evidence).
  - TDF + 3TC (or FTC) + dolutegravir or TDF + 3TC (or FTC) +EFV 400 mg/day may be used as alternatives to initiate ART (conditional recommendation, moderate-quality evidence).

Countries should discontinue stavudine use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).

Costs/Cost–effectiveness

In USA, wholesale acquisition cost of the FTC + TAF combination described in the application is US$ 1466 for 30 days' supply (30 tablets).

The application states that developing countries classified as low- or lower-middle-income by the World Bank, and countries with unmet HIV/AIDS disease burden, are designated as "access countries" and are charged only for production and related costs. The application also states that the cost of a 30-day supply of FTC + TAF to access countries is US$ 17 (US$ 204 per year).

By way of comparison, the WHO Global Price Reporting Mechanism reports that the median treatment cost per year in 2016 for FTC + TDF is US$ 55.10.

Availability

This product is currently licensed in Canada, Europe and USA.

Gilead has licensing agreements with generic drug manufacturers in China, India and South Africa, as well as the Medicines Patent Pool, allowing production and sale of generic versions of Gilead medicines in 112 developing countries.

Other considerations

N/A

Committee recommendations

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.

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Emtricitabine + rilpivirine + tenofovir alafenamide – rejection – EML

Emtricitabine + rilpivirine + tenofovir alafenamide **ATC Code: J05AR19**

Proposal

The application requested addition of a fixed-dose combination formulation of emtricitabine (FTC), rilpivirine (RPV) and tenofovir alafenamide (TAF) to the core list of the EML for the treatment of HIV infection in patients aged 12 years and above who are antiretroviral treatment (ART)-naive and have HIV1-RNA <100 000 copies/mL, and as replacement ART in patients with viral suppression (HIV1-RNA <50 copies/mL) on a stable ART regimen.

Applicant(s)

Gilead Sciences Inc., California, USA

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML

Section

6.4.2 Antiretrovirals – fixed-dose combinations

Dose form(s) and strength(s)

Tablet: 200 mg + 25 mg + 25 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

This was the first application seeking listing of FTC + RPV + TAF for treatment of HIV infection. The component medicines are not currently available individually on the EML.

In 2015, the Expert Committee considered an application seeking listing of a similar FDC formulation, incorporating tenofovir disoproxil fumarate (TDF). The application presented the results of the ECHO and THRIVE studies (*1*), which effectively compared RPV 25 mg and efavirenz 600 mg. Both treatment groups received a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone. The Expert Committee acknowledged that the data presented

in the application supported the efficacy of this FDC but noted that RPV is indicated only for patients with a low viral load (<100 000 copies/mL). The Committee considered that triaging patients according to baseline viral load, or switching regimens after achievement of viral suppression was not consistent with a public health approach and may not be feasible in resource-limited settings. In addition, the Committee noted that RPV would not be suitable for patients coinfected with tuberculosis and taking rifampicin.

The Committee noted that the proposed formulation included medicines that were not currently recommended in the WHO guidelines as first-line HIV treatment options and that there was insufficient evidence of a relevant clinical advantage over currently recommended first-line treatments already on the EML. Listing was not recommended (*2*).

Public health relevance (burden of disease)

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were in low- and middle-income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving ART in 2015 (*3*).

Summary of evidence – benefits (from the application)

The application presented evidence for the effectiveness of FTC + RPV + TAF using data from studies of the individual components.

For rilpivirine: Non-inferior efficacy of the regimen containing RPV 25 mg compared with that containing efavirenz (EFV) 600 mg was supported by the pooled results of the ECHO and THRIVE trials for virological outcomes at week 96 in patients with baseline viral load <100 000 copies/mL (83.7% vs 80.8% for RPV and EFV, respectively) (*1*). A study of a small number ($n = 36$) of adolescent patients, the PAINT trial, showed pharmacokinetic exposure, treatment response and tolerability of RPV to be comparable to that observed in adults (*4*). The SPIRIT study investigated non-inferiority of switching virologically supressed patients from a ritonavir-boosted protease inhibitor and a double-NRTI backbone to RPV and FTC + TDF as a simplified treatment regimen (*5*). At week 24, switching resulted in no significant difference in maintenance of virological suppression and met the criteria for non-inferiority.

For FTC + TAF, results from studies involving cobicistat (COBI) + elvitegravir (EVG) + FTC + TAF were presented (*6–8*). The findings of these studies are available in the summary for the COBI + EVG + FTC + TAF application. Bioequivalence between the proposed FDC and the FTC + TAF component of COBI + EVG + FTC + TAF and RPV was demonstrated in a small phase 1 study of 96 healthy subjects (*9*). The application also included results from two ongoing switching studies, where week 48 data suggested efficacy in terms of virological suppression being maintained with switching to FTC + RPV + TAF from regimens containing FTC + TDF. To date, these results have been reported only as a conference presentation (*10*).

Summary of evidence – harms (from the application)

Evidence for harms was taken from the comparison of TAF and TDF in combination with

cobicistat, elvitegravir and emtricitabine.

Renal effects: Compared with the TDF combination, the TAF combination was found to be associated with smaller mean serum creatinine increases (0.08 versus 0.12 mg/dL; $P < 0.0001$), and less proteinuria (median % change –3 versus 20; $P < 0.001$) at 48 weeks (*6*). The positive effects of the TAF combination on renal function were maintained at 96 weeks (*11*). Improvements in renal tubular biomarkers were greater in adolescents given the TAF combination than in those given the TDF combination (*7, 12*), and in patients switching from a TDF-containing regimen (*8, 13, 14*).

Bone effects: Compared with the TDF combination, the TAF combination was associated with a smaller decrease in bone mineral density (BMD) at lumbar spine (mean % change –1.30 versus –2.86; $P < 0.0001$) and hip (mean % change –0.66 versus –2.95; $P < 0.0001$) at 48 weeks (*6*). The effect with the TAF combination on lumbar spine BMD was greater after 96 weeks of treatment (mean % change –0.96% versus –2.79; $P < 0.001$) (*11*). In adolescent patients, median % change in spine BMD increased in patients in the TAF arm, while it decreased in patients in the TDF arm (1.25% versus –0.99%; $P < 0.009$) (*7, 12*). Patients switched from TDF-containing regimens to TAF-containing regimens also showed improvements in spine and hip BMD (*8, 13*).

The Expert Committee considered that the measured benefits of the TAF-combination in terms of renal function and bone effects are based on surrogate measures and, with the relatively short-term follow-up (48 weeks), that these may not translate in the longer term into benefits of the same magnitude in more patient-relevant clinical outcomes such as reduced risk of renal failure or fractures.

From the ECHO and THRIVE trials, the rilpivirine-treated group had a lower frequency of treatment-related grade 2–4 adverse events (17% vs 33%). The greatest differences between RPV and EFV treatment groups was seen with treatment-related psychiatric adverse events (16% vs 27%) and skin rash (5% vs 16%) (*1*).

Additional evidence (not in the application)

N/A

WHO guidelines

WHO's 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*15*) make the following recommendations for first-line ART in adults:

- First-line ART for adults should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI).
- TDF + lamivudine (3TC) (or emtricitabine (FTC)) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
- If TDF + 3TC (or FTC) + EFV is contraindicated or unavailable, one of the following alternative options is recommended:

- AZT + 3TC + EFV
- AZT + 3TC + NVP
- TDF + 3TC (or FTC) + NVP

(conditional recommendation, moderate-quality evidence).

- TDF + 3TC (or FTC) + dolutegravir or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternatives to initiate ART (conditional recommendation, moderate-quality evidence).

Countries should discontinue stavudine use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).

Costs/Cost–effectiveness

In USA, wholesale acquisition cost of the FTC + RPV + TAF combination described in the application is US$ 2345.87 for 30 days' supply (30 tablets).

The application stated that developing countries classified as low- or lower-middle-income by the World Bank, and countries with unmet HIV/AIDS disease burden, are designated as "access countries" and are charged only production and related costs. The application also stated that the price for a 30-day supply of the TAF-combination (presumably to access countries) is US$ 32 (US$ 384 per year).

By way of comparison, the WHO Global Price Reporting Mechanism reports that the median treatment cost per year in 2016 for the current preferred first-line ART (TDF + FTC + EFV) is US$ 77.12.

Availability

This product is currently licensed in Europe and USA.

Gilead has licensing agreements with generic drug manufacturers in China, India and South Africa, as well as the Medicines Patent Pool, allowing production and sale of generic versions of Gilead medicines in 112 developing countries.

The Expert Committee noted that relatively few (1500) adults have been treated with FTC + RPV + TAF to date.

Other considerations

Consistent with the findings of the 2015 Expert Committee, it was also the view of the current Expert Committee that assays required to determine baseline viral load and eligibility for treatment with this combination added complexity to treatment implementation from a public health perspective and may not be feasible in resource-limited settings.

Committee recommendations

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 <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.

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Tenofovir disoproxil fumarate – change: new indication – EML

Emtricitabine + tenofovir disoproxil fumarate– change: new indication – EML

Lamivudine + tenofovir disoproxil fumarate– change: new indication – EML

Tenofovir disoproxil fumarate **ATC Code: J05AF07**
Emtricitabine + tenofovir disoproxil fumarate **ATC Code: J05AR03**
Lamivudine + tenofovir disoproxil fumarate **ATC Code: J05AR12**

Proposal

Two applications sought extension to the current listings of single-agent tenofovir disoproxil fumarate (TDF) and the fixed-dose combinations of emtricitabine (FTC) + TDF and lamivudine (3TC) + TDF on the EML to include the new indication for use as oral pre-exposure prophylaxis (PrEP) of HIV infection.

Applicant(s)

WHO Department of HIV/AIDS, Ioannis Hodges-Mameletzis (all medicines)

Gilead Sciences Inc., California, USA (FTC + TDF only)

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML

Section

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors (TDF)

6.4.2 Antiretrovirals – fixed-dose combinations (FTC + TDC; 3TC + TDF)

Dose form(s) and strength(s)

TDF: Tablet: 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)

FTC + TDF: Tablet: 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)

3TC + TDF: Tablet: 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)

Core/Complementary

Core

Individual/Square box listing

Individual

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

This was the first time the Expert Committee had considered TDF-containing medicines for the new indication of pre-exposure prophylaxis for prevention of HIV infection.

TDF and FTC + TDF are currently included on the EML for the treatment and prevention of HIV infection. Prevention is specified as post-exposure prophylaxis and prevention of mother-to-child transmission. The current listing for FTC + TDF notes that FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, resistance patterns and clinical trials of antiretrovirals. This should be interpreted to mean that 3TC + TDF is included on the EML (by proxy).

Public health relevance (burden of disease)

Globally, the estimated annual number of new HIV infections among adults has remained reasonably static since 2010, at an estimated 1.9 million infections. No decrease or small declines (<5%) have been achieved in most world regions, while a 57% increase in new HIV infections was reported in eastern Europe and central Asia between 2010 and 2015. This represents a challenge for achievement of the milestone agreed by the United Nations General Assembly in 2016 – that is, to reduce new HIV infections to fewer than 500 000 globally by 2020 (*1, 2*).

In 2015, WHO recommended use of daily oral PrEP containing TDF (i.e. not limited to only FTC + TDF) for individuals at substantial risk of HIV infection as part of combination prevention approaches, based on clinical trial evidence supporting efficacy of TDF for PrEP across a variety of settings and populations. This recommendation was made available on an early-release basis, in advance of the 2016 revision of *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*3*). The rationale for the early release was to help countries anticipate the implications of the recommendation and allow them to initiate necessary steps to ensure that national standards for HIV prevention and treatment would keep pace with scientific developments (*4*).

Summary of evidence – benefits (from the application)

The application from the WHO Department of HIV/AIDS presented the findings of a systematic review and meta-analysis of 17 studies (14 randomized controlled trials (RCTs) and three observational, open-label extension cohort studies; more than 15 000 participants), investigating the effectiveness of PrEP using TDF either alone or in combination with FTC in people at substantial risk of HIV infection (*5*). Study populations included serodiscordant couples, people who inject drugs, men who have sex with men, female sex workers, transgender women, and heterosexual men and women. The quality of evidence for efficacy outcomes was rated as high following the GRADE approach.

Ten RCTs in the meta-analysis compared PrEP with placebo. A 51% reduction in risk of HIV infection was associated with PrEP (TDF +/– FTC) across populations (risk ratio (RR) 0.49;

95% confidence interval (CI) 0.33–0.73; *P* = 0.001). In studies that measured adherence, PrEP was found to be most efficacious in reducing risk of HIV infection in the subgroup with high (≥70% drug detection) adherence (RR 0.30; 95% CI 0.21–0.45; *P* < 0.0001). Among studies with low adherence, PrEP was not associated with a reduced risk of infection (RR 0.95; 95% CI 0.74–1.23; *P* = 0.7). There was no significant difference in risk reduction between PrEP regimens: TDF alone (RR 0.49; 95% CI 0.28–0.86; *P* = 0.001) and FTC+TDC (RR 0.51; 95% CI 0.31–0.83; *P* = 0.007).

Two RCTs compared PrEP with no PrEP and contributed HIV-infection data to the meta-analysis. PrEP was associated with an 85% reduction in the risk of HIV infection compared with delayed PrEP (RR 0.15; 95% CI:0.05–0.46; *P* = 0.001).

No studies involving 3TC + TDF were included in the systematic review. The application states that there have been two clinical studies of this combination for prevention of mother-to-child transmission of HIV, which provide indirect evidence and serve as "proof of principle" for use of this combination for PrEP.

The application from Gilead Sciences Inc. described efficacy results of the iPrEx (*6*) and the Partners PrEP (*7*) studies, both of which were included in the WHO-commissioned systematic review (described above).

The iPrEx study compared PrEP using FTC + TDV with placebo in HIV-negative men or transgender women who have sex with men. FTC + TDF was associated with a 44% reduction in the incidence of HIV compared with placebo (hazard ratio (HR) 0.56; 95% CI 0.37–0.85; *P* = 0.005). Efficacy was related to adherence, with patients with detectable study-drug levels having a relative risk reduction of 92% (95% CI 40–99%; *P* < 0.001) (*6*).

The Partners PrEP study compared PrEP using TDF alone, FTC + TDF and placebo in 4747 HIV-serodiscordant heterosexual couples in Kenya and Uganda. Compared with placebo, relative reductions in the incidence of HIV infection of 67% and 75%, respectively, were observed for TDF alone (HR 0.33; 95% CI 0.19–0.56; *P* < 0.001) and FTC + TDF (HR 0.25; 95% CI 0.13–0.45; *P* < 0.001). The difference between TDF and FTC + TDF with regard to HIV-protective effects was not significant (*7*).

Summary of evidence – harms (from the application)

The WHO-commissioned systematic review concluded that TDC-containing PrEP presented few significant safety risks and no evidence of behavioural risk compensation (*5*). Among 10 RCTs comparing PrEP with placebo, there was no difference in the rates of any adverse event (RR 1.01; 95% CI 0.99–1.03, *P* = 0.27). Similarly, there was no difference in rates of any grade 3 or 4 adverse events between PrEP and placebo groups (RR 1.02; 95% CI 0.92–1.13; *P* = 0.76). No increases in sexual risk behaviour, pregnancy-related adverse events or hormonal contraception effectiveness were associated with PrEP.

Participants randomized to PrEP had a higher risk of developing TDF- or FTC-resistance compared with placebo among those infected with HIV at the start of therapy (RR 3.34; 95% CI 1.11–10.06; *P* = 0.03). There was a greater risk of developing FTC-resistance than TDF-resistance.

The risk of drug resistance in the PrEP setting must be considered in the context of the prevention of HIV infection and the reduction in lifelong antiretroviral therapy (ART). The

risk of drug resistance due to ART is likely to be greater than the risk of drug resistance due to PrEP (*8*).

The application from Gilead Sciences Inc. described the known adverse effects of FTC + TDF on renal and bone health, and the events that occurred with greater frequency in patients given FTC + TDF treated in the RCTs and open-label extension trials (nausea, headache, weight loss). The application noted the findings in a meta-analysis by Fonner et al., which are the published results of the WHO-commissioned review described above (*9*).

Additional evidence (not in the application)

N/A

WHO guidelines

WHO's 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*3*) recommend that oral PrEP containing TDF be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).

"Substantial risk" is currently defined as HIV incidence around 3 per 100 person-years or higher in the absence of PrEP. Risk thresholds for offering PrEP are likely to vary on the basis of local considerations such as epidemiological factors, available resources, cost, feasibility and demand.

Costs/Cost–effectiveness

The application from the WHO Department of HIV/AIDS summarized the costs of TDF-containing PrEP products in low- and middle-income countries as follows:

Dose and pricing of generic ARTs for use in PrEP				
Product	***Dose(s) (mg)***	***Prior use in PrEP clinical trials***	***FPP pricing (median/unit; US$/year)***	***API pricing (median/kg; US$) (% of FPP price)***
TDF (30 count)	300	Yes	45.24	170 (41.3%)
TDF/FTC (30 count)	300/200	Yes; most PrEP data are from this product	67.20	170/250 (55%)
TDF/3TC	300/300	No data available	50.48	170/135 (65%)

FPP = finished pharmaceutical product; API = active pharmaceutical ingredient

The HIV incidence threshold for cost-saving implementation of PrEP will vary with the relative costs of PrEP versus HIV treatment and the expected effectiveness of PrEP. A systematic review of cost–effectiveness studies of PrEP concluded that providing PrEP to

populations at the highest risk of HIV exposure was the more cost-effective strategy (*10*).

The Gilead application stated that the wholesale acquisition cost of FTC + TDF in USA is US$ 1466 for 30 days' supply (30 tablets). It stated that developing countries classified as low- or lower-middle-income by the World Bank, and countries with unmet HIV/AIDS disease burden, are designated as "access countries", which are charged only for production and related costs. The application also stated that the price for a 30-day supply of FTC + TDF to access countries is US$ 20 (approximately US$ 240 per year).

The WHO Global Price Reporting Mechanism reports that the median treatment cost per year in 2016 for FTC + TDF is US$ 55.10.

Availability

There are several manufacturers of TDF-containing products for PrEP, many with WHO prequalification status.

There is some question regarding the ready availability of single-agent TDF products for treatment and prevention programmes, with low demand due to the availability of preferred fixed-dose combination formulations containing TDF.

To date, only FTC + TDF has approval from stringent regulatory authorities for use as PrEP.

Other considerations

N/A

Committee recommendations

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.

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

Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim – addition – EML and EMLc

Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim **ATC Code: to be assigned**

Proposal

The application requested addition of a fixed-dose combination formulation of isoniazid, pyridoxine, sulfamethoxazole and trimethoprim to the core list of EML and EMLc for the prevention of infections in adults and children living with HIV/AIDS.

Applicant(s)

Dr Marco Vitoria, WHO Department of HIV/AIDS

WHO technical department

WHO Department of HIV/AIDS

EML/EMLc

EML and EMLc

Section

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

Dose form(s) and strength(s)

Tablet (scored): 300 mg + 25 mg + 800 mg +160 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

WHO included this fixed-dose combination (FDC) of isoniazid (INH), pyridoxine (vitamin B6), sulfamethoxazole and trimethoprim (co-trimoxazole, CTX) in the 10th Invitation for Expression of Interest for prequalification of HIV medicinal products. A formulation manufactured by Cipla Ltd was added to the list of prequalified medicines on 21 December

2016.

Current WHO consolidated guidelines recommend both CTX preventive therapy (CPT) and INH preventive therapy (IPT) as part of the standard package of care available to prevent tuberculosis (TB), toxoplasmosis, pneumocystis, bacterial pneumonia, malaria and isosporiasis, and reduce mortality and hospitalizations among adults and children living with HIV/AIDS on the condition that active TB has been excluded (*1*). Vitamin B6 is recommended in all HIV-infected persons on INH to prevent peripheral neuropathy and other INH toxicities.

Public health relevance (burden of disease)

HIV infection increases the risk of TB 20–37-fold, depending on the severity of the HIV epidemic (*2*). WHO estimated that 10.4 million people developed TB in 2015, including 1.2 million persons living with HIV (PLHIV). TB was one of the top 10 causes of death worldwide in 2015 and responsible for more deaths than HIV and malaria. In 2015, 1.8 million people died from TB, including 0.4 million among PLHIV (*3*). The target population for this FDC is PLHIV in whom active TB has been excluded.

Summary of evidence – benefits (from the application)

CTX for prevention of *Pneumocystis jirovecii* pneumonia (PCP) and other opportunistic infections and INH plus vitamin B6 supplementation for TB have been evaluated and used in clinical practice for many years. The INH/B6/ CTX FDC was used as part of a clinical trial (the REALITY study) conducted in 1805 African patients, including 72 paediatric patients (aged 5–17 years) (*4*). Other use of the product has not been documented as the FDC is only now becoming commercially available.

The open-label REALITY trial (Reduction of EArly mortaLITY in HIV-infected adults and children starting antiretroviral therapy (ART)) was conducted to evaluate whether an enhanced package of infection prophylaxis at the time of ART initiation would reduce mortality in an African population. The study randomized ART-naive HIV-infected adults and children aged 5 years and above with CD4 <100 cells/mm3 to initiating ART with enhanced prophylaxis (continuous CTX plus 12 weeks' INH/B6 (antituberculosis) and fluconazole (anticryptococcal/anticandidiasis), 5 days' azithromycin (antibacterial/ antiprotozoal) and single-dose albendazole (anthelminthic), versus standard-of-care co-trimoxazole. INH/B6/CTX was formulated as a scored FDC tablet.

The study investigators concluded that, in HIV-infected adults and children over 5 years of age with CD4 <100 cells/mm3 enhanced prophylaxis at ART initiation, reduced early mortality from 14.4% to 11.0% over 96 weeks (25% relative reduction), and reduced adverse events and hospitalizations. The additional pill burden did not adversely affect viral load suppression and was reduced by a well-accepted FDC of CTX/INH/B6. The authors concluded that policy-makers should consider adopting and implementing this low-cost, broad infection prevention package, which could save 3.3 lives for every 100 individuals treated (*4*).

The results of the REALITY study are supportive of the use of INH/B6/CTX FDC in HIV-infected adults. The small number of paediatric patients enrolled in the study makes it

difficult to interpret efficacy results in patients aged 5–17 years, but the available data support use of a half-dose in patients under 12 years of age and weighing least 14 kg and use of the full dose in patients aged 12–17 years.

A review and commentary published in 2015 summarized the need for an FDC product that would include all the components of IPT and CPT in a single tablet (*5*). The authors concluded that IPT is a useful adjunct to ART in preventing TB in settings of high TB transmission but that long-term treatment is needed to maintain ongoing benefits. They found no evidence to suggest that IPT increased the risk of INH-resistant TB. In addition, they noted that CPT reduced mortality by 60% if started with ART at CD4 counts of 350 cells/mm3 or lower, regardless of geographical region. They noted that the benefits of continuing CPT were further supported by a randomized trial in Uganda and Zimbabwe of children infected with HIV, which showed that those who continued CPT after 2 years of ART had reduced hospitalizations for malaria, pneumonia, sepsis and meningitis.

Summary of evidence – harms (from the application)

All the component drugs of the INH/B6/CTX FDC have well-characterized toxicity and tolerability profiles. The combination of these drugs into the bioequivalent FDC does not alter the toxicity profile but is expected to improve tolerability by reducing pill burden.

A number of relevant drug–drug interactions are associated with the medicines included in the FDC, but these also apply to the medicines administered separately.

Additional evidence (not in the application)

A systematic review of 10 randomized controlled trials (7619 patients) comparing IPT with placebo in HIV-infected adults found that IPT was associated with a reduced risk of TB among all participants (relative risk (RR) 0.65; 95% confidence interval (CI) 0.51–0.84). IPT was also associated with a reduced risk of HIV disease progression among all participants (RR 0.69; 05% CI 0.48–0.99) (*6*).

A Cochrane systematic review of four randomized trials (1476 patients) comparing CTP with placebo in HIV-infected adults found that CTP was associated with a reduced risk of mortality (RR 0.69; 95% CI 0.55–0.87), morbid events (RR 0.76; 95% CI 0.64–0.9) and hospitalization (RR 0.66; 95% CI 0.48–0.92) (*7*).

WHO guidelines

The WHO 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* contain recommendations for the use of drugs for prevention and treatment of opportunistic infections such as PCP and serious bacterial infections (*1*). The Guidelines offer recommendations on CPT for HIV-infected adults, adolescents, children and infants.

The guidelines note that all HIV-infected adults, adolescents and children should be clinically screened for TB to identify those who should be either expedited for TB diagnosis or given preventive TB therapy. In the absence of a clinical suspicion of active TB, HIV-infected patients should be offered IPT. Pyridoxine is recommended in all HIV-infected persons on INH to mitigate toxicity.

Costs/Cost–effectiveness

There is no information on the cost of this FDC; however, the application estimates a cost of about US$15 per adult patient per year.

A number of economic analyses have considered the cost–effectiveness of elements of the proposed FDC. Yazdanpanah et al. reported that using CPT would cost US$ 200/life-year gained (*8*). Shrestha et al. used a Markov model to estimate the cost–utility of treating patients with INH for nine months, regardless of purified protein derivative (PPD) status, and arrived at a figure of US$ 106/quality-adjusted life-year (QALY) gained in Uganda. These authors found that this treatment approach would produce an additional 30 QALYs per 100 patients treated (*9*). Bell et al. used a Markov model to estimate that 6 months of IPT would save US$ 24 per primary or secondary case prevented (considering medical care and societal costs), increase life expectancy and quality-adjusted life expectancy, and reduce TB incidence (*10*).

In addition, the application argued that there may be cost savings related to the shipment and storage of FDC tablets and that a reduced pill burden for patients would improve compliance.

Availability

This FDC is currently being manufactured by Cipla Ltd. It received WHO prequalification status on 21 December 2016.

All the component medicines of INH/B6/CTX are off-patent and available from many generic suppliers. The FDC is currently under review by some national regulatory agencies; at the time of writing, however, it had not been reviewed by either the U.S. Food & Drug Administration or the European Medicines Agency.

Other considerations

N/A

Committee recommendations

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.

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6.4.3: Other antivirals

Oseltamivir - change: core to complementary list - EML and EMLc

Oseltamivir **ATC Code: J05AH02**

Proposal

The application proposed the deletion of oseltamivir for potentially severe or complicated illness due to confirmed or suspected influenza virus infection from the EML and EMLc.

Applicant(s)

Professor Chris Del Mar, Dr Peter Doshi, Professor Carl Heneghan, Dr Mark Jones, Dr Igho Onakpoya, Acute Respiratory Infections Cochrane Review Group.

WHO technical department

WHO Department of Infectious Hazard Management

EML/EMLc

EML and EMLc

Section

6.4.3 Other antivirals

Dose form(s) and strength(s)

Capsule: 30 mg, 45 mg, 75 mg

Oral powder: 12 mg/mL

Core/Complementary

Core

Individual/Square box listing

Individual

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

Oseltamivir was added to the EML in 2011, following the 2009 H1N1 influenza outbreak which was classified at the time as a public health emergency. Its listing included notes specifying the conditions of use: only in patients with severe or progressive clinical illness, with confirmed or suspected influenza, and in patients with confirmed or suspected but uncomplicated illness due to pandemic influenza virus infections who were in higher-risk groups (e.g. pregnant women and children under 2 years of age).

At that time, the effect of oseltamivir in reducing the complications of influenza was

reported in a pooled analysis of 10 manufacturer-sponsored randomized trials for the treatment of seasonal influenza (*1*). Enrolled patients were otherwise healthy unimmunized adults and adolescents, and specific patient groups defined as being at-risk of influenza (e.g. community-living elderly persons aged 65 years and above, patients with respiratory and/or cardiac disease).

The addition of oseltamivir to the EML was based on consideration of not only the randomized trials but also systematic reviews of observational studies. The meta-analysis of observational data examined was published as an independent systematic review of 74 studies (*2*). The few studies that reported effects with adjustment for confounders suggested that, in high-risk populations, oral oseltamivir may reduce mortality (3 studies; 681 patients; odds ratio (OR) 0.23; 95% confidence interval (CI) 0.13–0.43; low-quality evidence), hospitalization (4 studies; 150 710 patients; OR 0.75; 95% CI 0.66–0.89; low-quality evidence), and duration of symptoms (6 studies; 5842 patients; 33 hours; 95% CI 21–45; very low-quality evidence) compared with no treatment. The large effect on mortality was considered a key element in the decision, despite a high risk of bias in the observational studies of severely ill patients.

In 2013, the Expert Committee reviewed the available evidence and decided to retain oseltamivir on the list. Until that time, no randomized trials in patients with severe or complicated illness had been undertaken and this remains the case today. Further, numerous randomized trials of oseltamivir treatment had never been published. In 2014, however, their results become available as a result of protracted investigations and efforts by independent researchers to retrieve unpublished evidence. Fifty-three clinical trials of oseltamivir and zanamivir, cited in support of applications for regulatory approval, were included in a Cochrane systematic review; 46 of the trials were formally analysed (*3*).

In 2016, the Cochrane group published a systematic review of observational studies of oseltamivir in hospitalized patients with 2009/A H1N1 influenza infection (*4*). The summary data included 30 studies and 11 013 patients for whom individual participant data (IPD) and survival times were available. Also in 2016, an independent group of experts in complex survival analysis published a re-analysis of a UK observational study of oseltamivir in hospitalized patients with 2009/A H1N1 influenza infection (*5*). The data included 1391 patients with confirmed pandemic influenza A/H1N1 infection collected during 2009–2010 in the United Kingdom. Manufacturer-sponsored studies were also published, including an individual patient meta-analysis of observational data in hospitalized patients with 2009/A H1N1 influenza infection (*6*). This review included 29 234 patients, from 78 centres, for whom information on mortality was available. However, this represents only a fraction of the potentially available data: of 401 centres contacted, only 19% agreed to contribute data.

There were no randomized studies of patients with severe influenza, and evidence on the benefits of oseltamivir for severely ill patients was therefore limited to non-randomized observational studies, primarily of patients hospitalized with 2009/A H1N1 influenza infection. The observational studies reported mortality data.

Cumulative evidence for hospitalization and mortality over time in randomized (RCT) and non-randomized (NRS) studies is summarized in the following table:

*Available data**	*2010*		*2017*	
	No. of studies	*No. of patients*	*No. of studies*	*No. of patients*
RCTs – hospitalization	7 subgroups (from 10 studies)	1063	7	4 394
NRSs – mortality	3	681	30	11 013

* Data reflect number of studies and patients included in the meta-analyses comparing oseltamivir versus placebo for hospitalization (2010) or mortality (2017) outcomes.

Public health relevance (burden of disease)

Seasonal influenza is an acute respiratory infection caused by three types of influenza viruses – types A, B and C – which circulate in all parts of the world. While both A and B viruses cause outbreaks and epidemics only type A influenza viruses are known to have caused pandemics. Influenza type C infections are detected much less frequently and usually cause mild infections.

Illnesses range from mild to severe. Hospitalization and death are limited largely to high-risk groups. Worldwide, seasonal influenza epidemics are estimated to result in 3–5 million cases of severe illness and between 250 000 and 500 000 deaths annually. In industrialized countries, most deaths associated with influenza occur among people aged 65 years and above (*7*). Epidemics can result in high levels of absenteeism from school and work, with consequent productivity losses. The effects of seasonal influenza epidemics in developing countries are not fully known, but research estimates indicate that between 28 000 and 111 500 children under 5 years of age died from influenza-related lower respiratory tract infections in 2008 (*8*).

In healthy individuals, influenza is usually uncomplicated and self-limiting; treatment is therefore supportive and includes antipyretics, adequate fluid intake, rest, and staying away from work or school until 24 hours after resolution of fever to limit the spread of infection to others.

The most effective means of preventing the disease is vaccination.

Summary of evidence – benefits (from the application)

The evidence in the application has been complemented with additional evidence integrated by the EML Secretariat.

Benefits associated with oseltamivir have been summarized in five main comprehensive studies.

A 2014 systematic review of the efficacy of oseltamivir included clinical study reports (CSRs) from 46 published and unpublished randomized, placebo-controlled trials of oseltamivir (20 trials) and zanamivir (26 trials) and regulatory information (*3, 9*).

In treatment trials, oseltamivir was associated with a reduction by 16.8 hours of time to first

alleviation of symptoms in adults (95% CI 8.4–25.1 hours). A similar treatment effect was also associated with oseltamivir in otherwise healthy children (mean difference 29 hours; 95% CI 12–47 hours), but no significant effect was seen in children with asthma. For the outcome measure of admission to hospital, there was no difference between the treatment groups in adults (risk difference (RD) 0.15%; 95% CI –0.91% to 0.78%). There was no significant treatment effect in children either, or in prophylaxis trials for hospital admissions. Oseltamivir reduced investigator-mediated unverified pneumonia in adults (RD 1.00%; 95%CI 0.22–1.49%); the number needed to treat to benefit (NNTB) was 100 (95% CI 67–451). However, the effect was not statistically significant in trials that used more detailed diagnostic criteria for pneumonia, and none of the CSRs reported laboratory or diagnostic confirmation of pneumonia. There was no significant treatment effect for this outcome in children or in prophylaxis trials (*3, 9*).

Evidence from RCTs has been criticized for not being generalizable to the 2009 A/H1N1 influenza virus pandemic, as trials were conducted in patients with seasonal as opposed to pandemic influenza, which is more severe and associated with more frequent complications. However, the expectation of regulatory authorities and others is that the effects of these medicines demonstrated in clinical trials might be generalizable to other strains of influenza A and B.

Antiviral chemoprophylaxis is generally not recommended in WHO guidelines (*10*), and oseltamivir is not included in the EML for this indication. During pandemics, however, WHO guidelines recommend treatment in high-risk patients exposed to an individual infected with influenza.

Data on prophylactic use from the same systematic review (*3, 9*) showed that oseltamivir prevented influenza symptoms in adult individuals and households. Symptomatic influenza was reduced by 55% in individual participants (RD 3.05%, 95% CI 1.83–3.88%; NNTB 33, 95% CI 26–55) and by 80% in households (RD 13.6%, 95% CI 9.52–15.47%; NNTB 7, 95% CI 6–11). There was no significant effect on asymptomatic influenza and no evidence of reduced influenza transmission.

Since 2012, at least three IPD analyses of the potential effect of neuraminidase inhibitors (primarily oseltamivir) on mortality have been published, based on observational data from the 2009 H1N1 pandemic. Two analyses were published by independent groups (*4, 5*) and found no effect on mortality; the third, published by a group funded by the manufacturer of oseltamivir, reported a protective effect of neuraminidase inhibitors (*6*).

The manufacturer-funded study concluded: "Compared with no treatment, neuraminidase inhibitor treatment (irrespective of timing) was associated with a reduction in mortality risk (adjusted odds ratio (OR) 0.81; 95% CI 0.70–0.93; $P = 0.0024$)." (*6*). However, this analysis did not properly take into account the time-dependent nature of exposure to oseltamivir, thus possibly introducing immortal time bias (a type of time-dependent bias in cohort studies that consistently biases results in favour of the intervention, conferring a spurious advantage to the treated group) (*11*). Other important biases e.g. those receiving oseltamivir were younger and wealthier, thus at lower risk) have also been suggested (*12*).

The first independent study concluded: "After taking account of time-dependent bias and potential confounding variables, competing risks analysis of the IPD showed no evidence that oseltamivir reduced the risk of mortality (hazard ratio (HR) 1.03; 95% CI 0.64–1.65)." (*4*).

The second independent study, after also accounting for this time-dependent bias, reached similar conclusions: "There is no direct effect of NI (i.e. neuraminidase inhibitors) on the hospital death rate; the hazard ratio (HR) of NI was 1.03 (95% CI 0.64–1.66)." (*5*).

In 2010, the observational evidence used by WHO to inform its guideline recommendations suggested a possible large effect of oseltamivir on mortality when used in a pandemic setting (OR 0.23; 95% CI 0.13–0.43), based on low-quality evidence from three small studies (*2*). The manufacturer-sponsored study summarized above suggests a much smaller effect on mortality (OR 0.81) (*6*). The two independent studies suggest oseltamivir has no beneficial effect on mortality in hospitalized patients (*4, 5*). These findings are consistent with the 2014 systematic review of the entire randomized evidence base of oseltamivir, which concluded that there is a modest positive effect on the symptoms of influenza but that effects on more clinically important outcomes such as complications of influenza are unproven (*3, 9*).

Summary of evidence – harms (from the application)

The application described the safety findings for oseltamivir from the above-mentioned systematic review (*9*).

In the treatment of adults, oseltamivir was associated with an increased risk of nausea when compared with placebo (RD 3.66%, 95% CI 0.90 7.39%; number needed to treat to harm (NNTH) 28, 95% CI 14–112) and vomiting (RD 4.56%, 95% CI 2.39–7.58%; NNTH 22, 95% CI 14–42). Among children, oseltamivir induced vomiting compared with placebo (RD 5.34%, 95% CI 1.75–10.29%; NNTH 19, 95% CI 10–57).

In prophylaxis trials, oseltamivir increased the risk of psychiatric adverse events during the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07–2.76%; NNTH 94, 95% CI 36–1538). There was a dose–response effect for psychiatric events in two treatment trials of oseltamivir, given at standard (75 mg) and high (150 mg) doses twice daily ($P = 0.038$).

In prophylaxis studies, oseltamivir increased the risk of headaches on-treatment (RD 3.15%, 95% CI 0.88–5.78%; NNTH 32, 95% CI 18–115), renal events on-treatment (RD 0.67%, 95% CI −0.01% to 2.93%), and nausea on-treatment (RD 4.15%, 95% CI 0.86–9.51%; NNTH 25, 95% CI 11–116).

Before 2014 it was well known that oseltamivir could lead to nausea and vomiting but published reports of rarer adverse effects were too few to allow any robust conclusions. Independent analysis of the entire randomized evidence base has shown long-term exposure to oseltamivir (as may be the case in prophylaxis) can lead to neuropsychiatric and renal adverse effects.

Additional evidence (not in the application)

The Secretariat identified an additional individual patient data meta-analysis, funded by Roche Pharmaceuticals, of all randomized controlled clinical trials comparing oseltamivir with placebo for treatment of seasonal influenza in adults (*13*). The primary outcome was time to alleviation of symptoms, which included nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats. Compared with mortality and hospitalization, the clinical relevance of the outcome is doubtful. Primary analyses were

conducted on patients identified as influenza-infected by positive culture from a nasal or throat swab or by greater increase from baseline in antibody titre (the intention-to-treat infected (ITT-i) population). This represents an analysis of efficacy, measuring the effect of the intervention under "ideal" circumstances and thus maximizing the extent of potential benefit. Analyses were also repeated for the intention-to-treat (ITT) population, i.e. all treated participants.

In the ITT-i population, oseltamivir was associated with a 21% shorter time to alleviation of all symptoms compared with placebo (time ratio 0.79; 95% CI 0.74–0.85; $P < 0.0001$). In the ITT population, there was a 15% shorter time to alleviation for oseltamivir compared with placebo (time ratio 0.85; 95% CI 0.80–0.90; $P < 0.0001$). The treatment difference in median time to symptom alleviation was −25.2 hours (95% CI −36.2 to −16.0) and −17.8 hours (95% CI −27.1 to −9.3), respectively.

In the ITT population, for the more clinically relevant outcome of admission to hospitals, 25 (1.0%) of 2402 participants treated with oseltamivir had to be admitted to hospital for any cause versus 35 (2.7%) of 1302 participants given placebo (risk ratio (RR) 0.61; 95% CI 0.36–1.03; $P = 0.066$). This result was statistically significant in the ITT-i population: nine (0.6%) of 1591 participants were admitted to hospital versus 22 (1.7%) of 1302 participants given placebo, corresponding to an estimated 63% risk reduction (RR 0.37; 95% CI 0.17–0.81; $P = 0.013$) and a risk difference of −1.1% (95% CI −1.4 to −0.3).

The IPD meta-analysis confirmed that oseltamivir treatment resulted in an increased risk of nausea (6.2% in the placebo group compared with 9.9% in patients treated with oseltamivir (RD 3.7%; 95% CI 1.8–6.1%) and an increased risk of vomiting (3.3% vs 8.0%; RD 4.7%; 95% CI 2.7–7.3%).

WHO guidelines

WHO guidelines for pharmacological management of pandemic influenza A(H1N1) 2009 and other influenza viruses were issued in 2009, under emergency conditions. At that time, available data were limited to a few randomized and observational trials. The guidelines make the following recommendations:

- Patients who have severe or progressive clinical illness should be treated with oseltamivir (strong recommendation, low-quality evidence).
- In situations where oseltamivir is not available or not possible to use, *or* if the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir, patients who have severe or progressive clinical illness should be treated with zanamivir (strong recommendation, very-low-quality evidence).
- Patients not in "at risk" groups who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals (weak recommendation, low-quality evidence).
- Patients in "at risk" groups with uncomplicated illness due to influenza virus infection should be treated with oseltamivir or zanamivir. Treatment should be initiated as soon as possible following onset of illness (strong recommendation, very-low-quality evidence).

The guidelines also include recommendations for infection with influenza virus strains other than pandemic influenza A(H1N1) 2009 virus (*10*).

Costs/Cost–effectiveness

The cost of oseltamivir varies from US$ 10 to US$ 20 for a 5-day course (10 capsules). Costs may vary according to the country, the procurement system and emergency conditions (*14*).

Availability

Oseltamivir is available in most, if not all, countries through direct procurement or under emergency stockpile programmes.

Other considerations

Available evidence indicates that oseltamivir is associated with a positive effect on the symptoms of influenza but that beneficial effects on more clinically important outcomes such as hospital admissions and mortality are unproven. In terms of improved symptoms, however, the potential benefits of oseltamivir may be offset by the increase in adverse events.

Additional evidence indicates that there are no benefits of oseltamivir for symptomatic patients without confirmed influenza virus infection. In routine clinical practice, administration of oseltamivir should be driven primarily by rapid diagnostic testing or polymerized chain reaction assays; during pandemics, however, testing of all patients may not be possible.

The ratio of benefits (e.g. symptom duration) to harms (e.g. risk of nausea and vomiting) in oseltamivir-treated patients will depend on the proportion of the population with confirmed influenza infection and possibly the severity of the disease. Oseltamivir-treated patients who do not have true influenza will experience harms but will derive no clinical benefit from treatment.

There may be a role for oseltamivir in situations where there is a high probability of influenza virus infection being responsible for influenza-like illness, such as in pandemic settings. During a pandemic, early estimates of the expected burden of disease and severity will predict the central or marginal role of oseltamivir.

The Expert Committee noted that data on the use of oseltamivir in severely ill patients with respiratory complications in epidemics and pandemics came from observational studies, which are usually undertaken without protocols specifying standardized interventions, outcome assessments or data recording procedures. The Committee also noted that new randomized trials with oseltamivir are under way in various countries but have not yet been completed. The Committee considered the possible need for this medicine in severely ill patients and therefore the potential benefit of retaining oseltamivir on the EML and EMLc.

Committee recommendations

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 managent of severe influenza is currently under development.

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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 – rejection – EML

Tenofovir alafenamide **ATC Code: J05AF13**

Proposal

The application requested 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.

Applicant(s)

Gilead Sciences Inc., California, USA

WHO technical department

WHO Global Hepatitis Programme

EML/EMLc

EML

Section

6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

Dose form(s) and strength(s)

Tablet: 25 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

This was the first application seeking listing of tenofovir alafenamide (TAF) for chronic hepatitis B (CHB).

An alternative tenofovir salt, tenofovir disoproxil fumarate (TDF), was added to the EML for this indication in 2015 (*1*). The recommendation to add TDF was based on evidence from randomized controlled trials supporting the role of TDF in various CHB treatment regimens, significant public health need, and the inclusion of TDF in 2015 WHO CHB treatment guidelines (*2*).

Public health relevance (burden of disease)

Globally, it is estimated that 240 million people are chronically infected with hepatitis B, particularly in low- and middle-income countries. Prevalence is highest in sub-Saharan Africa and east Asia, where up to 10% of the adult population is affected. Complications of hepatitis B infection, including cirrhosis and hepatocellular carcinoma, are responsible for an estimated 650 000 deaths per year (*2*).

Summary of evidence – benefits (from the application)

Antiviral activity of TAF over a wide range of doses was found to be comparable to that of TDF 300 mg in patients with CHB. At doses of 25 mg or less, TAF was associated with significantly reduced tenofovir exposure compared with TDF, and the 25-mg dose was selected for development in phase 3 trials (*3*).

The application presented the findings of two phase 3, randomized, double-blind, non-inferiority studies comparing TAF 25 mg and TDF 300 mg in 1298 hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients with CHB (*4, 5*). The primary end-point in each study was the proportion of patients with hepatitis B virus DNA <29 IU/mL at week 48, with a prespecified non-inferiority margin of 10%. The proportion of patients with alanine aminotransferase (ALT) normalization at week 48 was another measured outcome.

There was no significant difference in the proportion of HBeAg-negative patients receiving TAF or TDF who achieved the primary end-point (94% vs 93%, difference 1.8%; 95% confidence interval (CI) –3.6 to 7.2; $P = 0.47$). In HBeAg-positive patients, the proportions were lower but there was no significant difference (64% vs 67%, difference -3.6%; 95% CI –9.8 to 2.6; $P = 0.25$). In both studies, patients in the TAF group achieved significantly higher rates of ALT normalization when measured using American Association for the Study of Liver Diseases (AASLD) criteria. Differences were not significant when ALT normalization was measured using less stringent central laboratory criteria. Longer-term follow-up is planned.

Summary of evidence – harms (from the application)

Clinically relevant adverse events involving renal abnormalities and bone toxicity have been associated with TDF (*3*).

Safety outcomes from the two above-mentioned phase 3 studies indicated that most adverse events associated with TAF were of mild to moderate intensity; the commonest were headache, nasopharyngitis and upper respiratory tract infection (*4, 5*). The incidence of serious adverse events, and discontinuations due to adverse events, was low and similar across treatment groups.

Compared with TDF, TAF was associated with smaller increases in serum creatinine from baseline to week 48. The difference was significant only in the study of HBeAG-positive patients. Falls in estimated glomerular filtration rate (eGFR) were significantly smaller in the TAF group compared with the TDF group in both studies, and TAF was also shown to be associated with significantly smaller changes in proteinuria markers for renal tubular function.

TAF was associated with significantly smaller reductions in hip and spine bone mineral

density compared with TDF (4, 5). TAF was also associated with significantly smaller changes in some biomarkers of bone resorption and formation compared with TDF from baseline to week 48.

For further investigation of bone safety with TAF, pooled analyses of the phase 3 studies have been undertaken; to date, findings have been reported only as conference posters and oral presentations but are in line with the results of the primary analyses (*6–8*).

Additional evidence (not in the application)

Tenofovir alafenamide is a pro-drug of tenofovir, which has been associated with reduced plasma levels of the parent nucleotide at doses considerably lower than the approved dose of TDF. TDF has been associated with renal toxicity linked to active renal secretion via organic anion transporters (OAT) and higher exposure of renal proximal tubules to tenofovir. TAF has not been shown to interact with renal transporters, nor has there been OAT-dependent toxicity, suggesting a potential advantage of TAF over TDF in terms of renal safety (*9*). WHO's 2015 *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection* identified the need to establish the long-term safety, efficacy and toxicity of TAF versus TDF in patients with CHB infection, with or without HIV coinfection (*2*).

WHO guidelines

WHO's 2015 *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection* (*2*) make the following recommendations with regard to the parent nucleotide, tenofovir:

- In all adults, adolescents and children aged 12 years or more in whom antiviral therapy is indicated, a nucleoside/nucleotide analogue with a high barrier to drug resistance (tenofovir or entecavir) is recommended. Entecavir is recommended in children aged 2–11 years (strong recommendation, moderate-quality evidence).
- In HBV/HIV coinfected adults, adolescents and children aged 3 years or more, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate antiretroviral therapy (strong recommendation, moderate-quality evidence).
- In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir is recommended (strong recommendation, low-quality evidence).

Tenofovir dosages recommended in the WHO Guidelines correspond with the available dosages of TDF.

WHO Guidelines recognize TAF as an orally bioavailable prodrug of tenofovir that may be associated with less renal and bone toxicity then TDF, and identify the research gap in needing to investigate TAF's long-term safety, efficacy and toxicity.

Costs/Cost–effectiveness

The cost of TAF described in the application is US$ 10 for 30 days' supply (US$ 120 per

year). This is described as a no-profit price and does not include distribution and other related costs.

In comparison, the WHO Global Price Reporting Mechanism reports the median treatment cost per year for TDF 300 mg as US$ 32.24 in 2016.

Availability

Gilead has licensing agreements with generic drug manufacturers in China, India and South Africa, as well as the Medicines Patent Pool, allowing production and sale of generic versions of Gilead medicines in 112 developing countries.

Other considerations

N/A

Committee recommendations

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.

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6.4.4.2: Medicines for hepatitis C

Elbasvir + grazoprevir – rejection – EML

Elbasvir + grazoprevir **ATC Code: J05AX68**

Proposal

The application requested 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.

Applicant(s)

Dr Andrew Hill, University of Liverpool

WHO technical department

WHO Global Hepatitis Programme

EML/EMLc

EML

Section

6.4.4.2 Medicines for hepatitis C – Fixed-dose combinations

Dose form(s) and strength(s)

Tablet: 50 mg + 100 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Neither this fixed-dose combination (FDC) nor its individual components have been previously considered by the Expert Committee for addition to the EML.

Public health relevance (burden of disease)

Most recent analyses of the global prevalence of chronic hepatitis C indicate that some 115 million persons are HCV antibody-positive, of whom approximately 80 million are chronically infected (*1*). Prevalence varies greatly by region and population, with the highest burden of chronic infection in sub-Saharan Africa and south and east Asia.

Data from the Global Burden of Disease study indicates that the annual number of deaths attributable to HCV has been steadily increasing, from around 330 000 in 1990 to more than 700 000 in 2013 (*2*). This reflects the lag time between infection and the development of complications such as liver cirrhosis and hepatocellular carcinoma. The number of deaths is projected to increase through several more decades unless there is a rapid scaling-up of accessibility to treatment (*3*).

Scaling-up of screening and treatment using efficacious direct-acting antiviral (DAA) regimens has the potential to reduce the incidence of liver-related complications and mortality in individuals with HCV infection (*4, 5*). Further, while several new DAA combinations have shown excellent sustained viral response rates at 12 weeks (SVR12), certain groups, including patients who have previously failed treatment, have developed cirrhosis or renal failure, or are coinfected with HIV, remain difficult to treat. Many DAA-based regimens are not equally effective across all HCV genotypes.

The availability of effective, well-tolerated, once-daily (preferably), pan-genotypic and affordable DAAs can facilitate the scaling-up of public health programmes to address HCV, particularly in resource-limited settings where the burden of disease is greatest.

Summary of evidence – benefits (from the application)

Genotype 1

Eleven phase 2 and 3 trials evaluated the efficacy of elbasvir + grazoprevir (+/– ribavirin (RBV)) in a total of 1894 individuals with HCV genotype 1: C-SURFER (*6*), C-EDGE H2H (*7*), C-EDGE TE (*8*), C-EDGE TN (*9*), C-EDGE C0-INFECTED (*10*), C-EDGE CO-STAR (*11*), C-WORTHTY (*12, 13*), C-SALVAGE (*14*), C-SWIFT (*15*), and C-SWIFT-FINAL (*16*). The total cohort included both treatment-naive and treatment-experienced patients, patients coinfected with HIV and patients with chronic kidney disease. From the intention-to-treat analyses of these trials, 1809 of the 1894 patients achieved a sustained virological response after 12 weeks of treatment (SVR12 95.5%; 95% confidence interval (CI) 94.5–96.4%).

Genotype 4

Six phase 2 and 3 trials evaluated the efficacy of elbasvir + grazoprevir (+/– RBV) in 126 patients with HCV genotype 4 disease: C-EDGE H2H (*7*), C-EDGE TE (*8*), C-EDGE TN (*9*), C-EDGE CO-INFECTED (*10*), C-EDGE CO-STAR (*11*), and C-SCAPE (*17*). Like the genotype 1 studies, the total cohort again included treatment-naive and treatment-experienced patients and patients coinfected with HIV. From the intention-to treat-analyses of these trials, SVR12 was achieved in 118 of 126 patients (93.7%; 95% CI 87.9–97.2%).

Special populations

In the C-WORTHY (*13*) and C-EDGE CO-INFECTED (10) trials. 227 treatment-naive patients coinfected with HCV and HIV received elbasvir + grazoprevir for 12 weeks. SVR12 was achieved in 95.3% of individuals.

The C-SURFER trial (*6*) assessed the efficacy and safety of elbasvir + grazoprevir in 122 patients with stage 4 or 5 chronic kidney disease and HCV genotype 1 infection. SVR12 was achieved in 94.3% of individuals. No dosage adjustments are recommended for patients with renal impairment (*18*).

Efficacy of elbasvir + grazoprevir was evaluated in 201 IV drug users using opioid agonist therapy (*11*). SVR12 was achieved in 91.5% of individuals. Five individuals did not achieve SVR12 because of HCV reinfection. When reinfection was counted as success, SVR12 was achieved in 94.0% of individuals.

The application also presented the findings of trials of elbasvir + grazoprevir in other HCV genotypes. As EML listing was not sought for use in these other genotypes, the results are not reported here.

Summary of evidence – harms (from the application)

Safety data from the phase 2 and 3 studies indicate few discontinuations due to adverse events from elbasvir + grazoprevir, and a rate of serious adverse events comparable to that in other treatment regimens. No deaths attributable to the study drug were observed in the trials. As with other DAAs, the most frequently reported adverse effects were headache, nausea, fatigue, decreased appetite, anaemia, pyrexia and ALT elevations.

Concurrent use of elbasvir + grazoprevir with most HIV-protease inhibitors is contraindicated because of elevated elbasvir + grazoprevir plasma concentrations and alanine aminotransferase levels. Efavirenz has been shown to reduce elbasvir + grazoprevir concentrations by up to 80% and its concurrent use is also contraindicated. The pharmacokinetic enhancers ritonavir and cobicistat should be used with caution (*18*).

Other agents involved in clinically relevant drug–drug interactions with elbasvir + grazoprevir include ciclosporin and strong inducers and inhibitors of cytochrome P450 3A4, which can affect plasma concentration and lead to reduced therapeutic effects or increased adverse events (*19*).

Additional evidence (not in the application)

There is some evidence that the presence of baseline non-structural protein 5A (NS5A) resistance-associated variants (RAVs) in the treated population can be a treatment effect modifier in some patients. Individuals with genotype 1a infection were found to have a lower SVR when baseline NS5A RAVs to elbasvir were detected (69%, versus 96% when NS5A RAVs were not detected). This difference in treatment effect was not observed in individuals with genotype 1b infection (*20*).

WHO guidelines

Elbasvir + grazoprevir was not considered for inclusion in the 2016 update of the WHO *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection* (*21*) as it did not have stringent regulatory approval at the time. The Guidelines Development Group noted that the initial available data suggested efficacy of elbasvir + grazoprevir in the treatment of HCV, including in patients with HIV coinfection and/or renal impairment.

The guidelines noted data suggesting that some populations may not benefit from the elbasvir + grazoprevir combination. The presence of baseline NS5A resistance, which occurs in about 12% of patients, led to a marked decrease in SVR compared with

genotype 1a-infected patients without baseline resistance (69% vs 96%, respectively). This combination has not been considered in the guidelines as it had not received stringent regulatory approval at the time of the Guidelines Development Group meeting.

Costs/Cost–effectiveness

The USA wholesale acquisition cost for a 12-week course of elbasvir + grazoprevir is estimated to be US$ 54 000. Original wholesale costs for other DAAs currently included on the EML were significantly higher at US$ 150 000 (simeprevir + sofosbuvir), US$ 94 000 (ledipasvir + sofosbuvir) and US$ 147 000 (daclatasvir + sofosbuvir) (*18*). In comparison, the cost of a 12-week treatment course of elbasvir +grazoprevir in the United Kingdom is £36 500 (*22*).

It is not known whether Merck Sharp & Dohme, manufacturer of elbasvir + grazoprevir, have any access strategies in place for facilitating access to this product in low- and middle-income countries.

Availability

This FDC is produced by Merck Sharp & Dohme.

Other considerations

The Committee noted that other DAA FDCs in regulatory pipelines are pan-genotypic and require shorter duration of treatment (8 weeks).

Committee recommendations

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.

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Sofosbuvir + velpatasvir – addition – EML

Sofosbuvir + velpatasvir — ATC Code: J05AX69

Proposal

Two applications sought 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, genotypes 1 to 6, in adults.

Applicant(s)

Dr Andrew Hill, University of Liverpool

Gilead Sciences Inc., California, USA

WHO technical department

WHO Global Hepatitis Programme

EML/EMLc

EML

Section

6.4.4.2 Medicines for hepatitis C – fixed-dose combinations

Dose form(s) and strength(s)

Tablet: 400 mg + 100 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

The fixed-dose combination (FDC) of sofosbuvir + velpatasvir has not been previously considered by the Expert Committee for addition to the EML.

A single-agent formulation of sofosbuvir, and an FDC of ledipasvir + sofosbuvir were among six direct-acting antivirals (DAAs) for treatment of hepatitis C added to the core list of the EML in 2015.

Currently, no single-agent formulation of velpatasvir is marketed or available.

Public health relevance (burden of disease)

Most recent analyses of the global prevalence of chronic hepatitis C virus (HCV) indicate

that an estimated 115 million persons are HCV antibody-positive, of whom approximately 80 million are chronically infected (*1*). Prevalence varies greatly by region and population, with the highest burden of chronic infection in sub-Saharan Africa and south and east Asia.

Data from the Global Burden of Disease study indicates that the annual number of deaths attributable to HCV has been steadily increasing, from around 330 000 in 1990 to more than 700 000 in 2013 (*2*). This reflects the lag time between infection and the development of complications such as liver cirrhosis and hepatocellular carcinoma. The number of deaths is projected to increase through several more decades unless there is a rapid scaling-up in accessibility to treatment (*3*).

Scaling-up of screening and treatment using efficacious DAA regimens has the potential to reduce the incidence of liver-related complications and mortality in individuals with HCV infection (*4, 5*). Further, while several new DAA combinations have shown excellent sustained viral response rates at 12 weeks (SVR12), certain groups, including patients who have previously failed treatment, have developed cirrhosis or renal failure, or are coinfected with HIV, remain difficult to treat. Many DAA-based regimens are not equally effective across all HCV genotypes.

The availability of effective, well-tolerated, once-daily (preferably) pan-genotypic and affordable DAAs can facilitate the scaling-up of public health programmes to address HCV, particularly in resource-limited settings where the burden of disease is greatest.

Summary of evidence – benefits (from the application)

The characteristics and outcomes (in terms of SVR12) of the phase 3 studies that have evaluated the efficacy of sofosbuvir + velpatasvir, with or without ribavirin, for HCV genotypes 1-6 are summarized in the table below. High SVR12 rates have been observed with sofosbuvir + velpatasvir over 12 weeks across all genotypes, in both treatment-naive and treatment-experienced patients, patients with and without cirrhosis (compensated and decompensated), and patients with HCV/HIV co-infection. Both applications presented the results of the ASTRAL-1 (*6*), ASTRAL-2 (*7*), ASTRAL-3 (*7*), ASTRAL-4 (*8*) and ASTRAL-5 (*9, 10*) studies.

Efficacy outcomes of the phase 2 and 3 studies are summarized in detail in Application 1 by genotype and in Application 2 by trial. In all studies and for all genotypes, treatment with sofosbuvir + velpatasvir was shown to be associated with SVR12 rates in excess of 90%.

Genotype	*Trials included*	*Patient characteristics*	*Interventions*	*SVR12/Total (%)*
1	ASTRAL-1 ASTRAL-4 ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV-coinfected	SOF + VEL (12–24 weeks)	586/612 (95.8%) 95% CI 93.8–97.1%
2	ASTRAL-1 ASTRAL-2 ASTRAL-4 ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV-coinfected	SOF + VEL ± RBV (12–24 weeks)	259/261 (99.2%) 95% CI 97.1–>99.9%
3	ASTRAL-3 ASTRAL-4 ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV-coinfected	SOF + VEL ± RBV (12–24 weeks)	299/328 (91.2%) 95% CI 87.6–93.8%
4	ASTRAL-1 ASTRAL-4 ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV-coinfected	SOF + VEL ± RBV (12–24 weeks)	128/128 (100.0%) 95% CI 96.5–100.0%
5	ASTRAL-1	TN & TE	SOF + VEL (12 weeks)	34/35 (97.1%) 95% CI 84.2–>99.9%
6	ASTRAL-1 ASTRAL-4	TN & TE, cirrhosis, decompensated cirrhosis	SOF + VEL (12 weeks)	42/42 (100.0%) 95% CI 90.0–100.0%
Total	All trials above	All above characteristics included	SOF + VEL ± RBV (12–24 weeks)	1348/1406 (95.9%) 95% CI 94.7–96.8%[a]

[a] No meta-analysis performed – simple addition of trial results.

Abbreviations: TN treatment-naïve; TE treatment-experienced; RBV ribavirin; SOF sofosbuvir; VEL velpatasvir; CI confidence interval

(Source: Application 1)

Efficacy in special populations

ASTRAL-5 evaluated the efficacy of sofosbuvir + velpatasvir in 106 patients coinfected with HCV and HIV (*9, 10*). SVR12 was achieved in 95.3% of individuals. Sofosbuvir + velpatasvir may be given with most antiretroviral regimens, although concomitant use with efavirenz, etravirine, nevirapine or ritonavir-boosted tipranavir is not recommended. Use in combination with regimens containing tenofovir disoproxil fumarate should be undertaken with caution (*11*).

ASTRAL-4 evaluated efficacy of sofosbuvir + velpatasvir with or without ribavirin, in patients with decompensated cirrhosis (*8*). For the regimens of sofosbuvir + velpatasvir + ribavirin for 12 weeks, and sofosbuvir + velpatasvir alone for 12 or 24 weeks, the respective

SVR12 rates were 94%, 83% and 86%.

Virological failure and resistance

Treatment regimens involving sofosbuvir + velpatasvir appear to have a high barrier to viral resistance. The impact of baseline resistance-associated variants (RAVs) on treatment outcome and emergence of RAVs at relapse of patients was evaluated in a pooled analysis of the ASTRAL 1–4 studies (*12*). Among genotype 1–6 patients, 16–70% were observed to have non-structural protein 5A (NS5A) RAVs at baseline. In patients with genotypes 1, 2, 4, 5, and 6 HCV treated with sofosbuvir + velpatasvir, no impact of NS5A RAVs on SVR12 rates was observed. For genotype 3 patients with NS5A RAVs, SVR12 rates were 88%.

Summary of evidence – harms (from the application)

Safety data from the phase 2 and 3 trials of sofosbuvir + velpatasvir are summarized in the following tables from Application 1:

Phase 2 trials

Reference	*Genotypes*	*Total no. of patients*	*D/C due to AE, n (%)*	*Serious AE, n (%)*	*Deaths, n (%)*
(13)	1, 3	161	0	3 (2%)	0
(14)	1, 2, 3, 4, 5, 6[a]	377	1 (<1%)	7 (2%)	1 (<1%)
(15)	1, 3	321	1 (<1%)	8 (3%)	0
Total		859	2 (<1%)	18 (2%)	1 (<1%)

[a] Very few patients with genotypes 4, 5 or 6 included; efficacy results not available by genotype.

Abbreviations: AE adverse event; D/C discontinuation

Phase 3 trials

Study, Reference	*Genotypes*	*Total no. of patients*	*D/C due to AE, n (%)*	*Serious AE, n (%)*	*Deaths, n (%)*
ASTRAL-1 (*6*)	1, 2, 4, 5, 6	624	1 (<1%)	15 (2%)	1 (<1%)
ASTRAL-4 (*8*)	1, 2, 3, 4, 6	267	9 (3%)	47 (18%)	9 (3%)
ASTRAL-5 (*9*)	1, 2, 3, 4	106	2 (2%)	2 (2%)	0
ASTRAL-2 (*7*)	2	134	1 (<1%)	2 (1%)	2 (1%)
ASTRAL-3 (*7*)	3	277	0	6 (2%)	0
Total		1408	13 (<1%)	72 (5%)	12 (<1%)

Abbreviations: AE, adverse event; D/C, discontinuation

These data show few discontinuations due to adverse events and a rate of serious AEs similar to that with other regimens. None of the deaths observed was considered to be related to the study drug. The higher rate of adverse events and deaths in the ASTRAL-4 study is likely to be related to the enrolment of individuals with decompensated cirrhosis.

The most common adverse events observed with sofosbuvir + velpatasvir, and seen with similar incidence in placebo-treated patients, were headache, fatigue, nasopharyngitis and nausea (*16*).

Compared with placebo-treated patients (ASTRAL-1) and patients treated with ribavirin-containing regimens (ASTRAL-2 and-3), patients treated with sofosbuvir + velpatasvir showed improvements in patient-reported outcome scores for health-related quality-of-life measures (*17, 18*). Improvements were observed within the first 4 weeks of treatment and continued during and after the course of treatment.

Additional evidence (not in the application)

N/A

WHO guidelines

Sofosbuvir + velpatasvir was not considered for inclusion in the 2016 update of the WHO *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection* (*19*) as it did not have stringent regulatory approval at the time. The Guidelines Development Group noted that the available phase 3 data suggested potential for sofosbuvir + velpatasvir as a pan-genotypic regimen.

Sofosbuvir + velpatasvir is recommended in both European and USA 2016 guidelines for treatment of patients with HCV genotypes 1–6 (*11, 20*).

Costs/Cost–effectiveness

The USA wholesale acquisition cost for a 12-week course of sofosbuvir + velpatasvir is estimated to be US$ 74 670. Original wholesale costs for other DAAs currently included on the EML were significantly higher at US$ 150 000 (simeprevir + sofosbuvir), US$ 94 000 (ledipasvir + sofosbuvir) and US$ 147 000 (daclatasvir + sofosbuvir). The estimated wholesale cost for elbasvir + grazoprevir is US$ 54 000, although it is noted that elbasvir + grazoprevir is indicated for use only in patients with genotypes 1 and 4 HCV.

Application 2 (Gilead Sciences) stated that developing countries classified as low- or lower-middle-income by the World Bank, and countries with significant unmet HCV disease burden, are designated as "access countries", which are charged only for production and related costs. Its suggested government price for 12 weeks' supply of sofosbuvir + velpatasvir in access countries is US$ 900.

Availability

This product is currently licensed in Australia, Canada, Europe and USA.

Gilead has licensing agreements with generic drug manufacturers in India, allowing production and sale of generic versions of this medicine in 101 developing countries.

Other considerations

The Expert Committee noted the potential for drug–drug interactions if sofosbuvir + velpatasvir is co-administered with certain antiretroviral agents and the need for dosage adjustments in some situations.

Committee recommendations

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.

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6.5: Antiprotozoal medicines

6.5.3: Antimalarial medicines

6.5.3.1: For curative treatment

Artesunate + pyronaridine – addition – EML and EMLc

Artesunate + pyronaridine tetraphosphate ATC Code: P01BF06

Proposal

The application requested addition of a fixed-dose combination formulation of artesunate (A) + pyronaridine tetraphosphate (P) 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.

Applicant(s)

Shin Poong Pharmaceuticals

WHO technical department

WHO Global Malaria Programme

EML/EMLc

EML and EMLc

Section

6.5.3.1 For curative treatment

Dose form(s) and strength(s)

Tablet: 60 mg + 180 mg

Granules: 20 mg + 60 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Currently, the fixed-dose combination (FDC) artemisinin-combination treatments (ACTs) included in the EML are: artemether + lumefantrine (A+L), artesunate + amodiaquine (AS+AQ) and artesunate + mefloquine (AS+MQ).

Public health relevance (burden of disease)

It is estimated that a cumulative 1.2 billion fewer malaria cases and 6.2 million fewer malaria deaths occurred globally between 2001 and 2015 than would have occurred if had incidence and mortality rates remained unchanged since 2000. Of the estimated 6.2 million fewer deaths, about 5.9 million (95%) were in children aged under 5 years.

By 2015, it was estimated that the number of malaria cases had declined to 214 million (range 149–303 million), and the number of deaths to 438 000 (range 236 000–635 000). The number of malaria deaths in children aged under 5 years had declined to 306 000 (range 219 000–421 000) in 2015.

The global burden of mortality is dominated by countries in sub-Saharan Africa. Decreases in case incidence and mortality rates were slowest in countries that had the largest numbers of malaria cases and deaths in 2000 (*1*).

Summary of evidence – benefits (from the application)

P. falciparum studies

The application presented the results of three phase 3 clinical trials of artesunate + pyronaridine (A+P) compared with AS+MQ (*2*), and A+L (3*, 4*) in a total of 2803 children and adults with acute, uncomplicated *P. falciparum* malaria in Africa, south-east Asia and India. The primary end-point was polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological response (ACPR) on day 28 in the efficacy-evaluable (EE) population. Non-inferiority to the relative comparators was assumed if the lower limit of the two-sided 95% confidence interval (CI) for the difference in PCR-adjusted ACPR was greater than –5% (*2, 3*) or greater than –10% (*4*).

For the comparison with AS+MQ, results at day 28 showed PCR-adjusted ACPR rates of 99.2% (95% CI 98.3–99.7%) and 97.8% (95% CI 95.8–99,1%). The treatment difference was 1.4% (95% CI 0.0–3.5%; *P* = 0.05), meeting the predefined criteria for non-inferiority. Non-inferiority was also met for the comparisons with A+L. The PCR-corrected ACPR rates at day 28 for A+P and A+L were 99.5% and 99.2% (difference= 0.3%; 95% CI --0.7% to 1.8%; *P* = 0.578); and 97.1% and 98.8% (difference = –1.8%%; 95% CI –4.3% to 1.6%; *P* = 0.22). In addition, A+P was found to be non-inferior to the comparator treatments for the secondary end-point of PCR-adjusted ACPR at 42 days.

New infection or recrudescence rates based on Kaplan–Meier estimates were statistically significantly lower with A+P compared with AS+MQ through day 42 (*P* = 0.049). For the comparison with A+L, no statistically significant difference was found between groups through day 28 or day 42 (*2–4*).

In an integrated analysis of all A+P and comparator groups of phase 3 patients, the intention-to-treat (ITT) population was considered the primary analysis population, in contrast to the individual studies, given the variability of the EE population criteria across studies. No notable differences in PCR-adjusted ACPR were observed between the P+A group and the A+L or AS+MQ treatment groups at any time point in the ITT population (*5*).

P. vivax studies

One study compared the efficacy and safety of A+P with chloroquine in subjects with acute, uncomplicated *P. vivax* malaria (*6*).

Results at day 14 showed crude cure rates for A+P and chloroquine of 99.5% and 100% in the EE population (children and adults), which was the primary end-point in that study. Results were maintained in the ITT population. A high crude cure rate (95.5%) was still observed at day 42.

Summary of evidence – harms (from the application)

The safety database for the phase 2/3 A+P clinical programme included 3017 subjects who received at least one dose of A+P across seven phase I, two phase II, and five phase III studies or, in the case of the mass balance study, pyronaridine alone. The adverse event profile of A+P in the individual studies and in the integrated analysis of all phase 2/3 studies was consistent with profiles reported for pyronaridine and artemisinins as monotherapy (*7–10*). The most common adverse events were headache (3.0%), eosinophilia (2.5%), neutropenia (1.9%), anaemia (1.6%), increased platelet count (1.4%), vomiting (2.2%) and abdominal pain (1.4%), bradycardia (1.1%), transaminase increases (1.6% alanine aminotransferase/1.8% aspartate aminotransferase) and hypoglycaemia (1.0%).

Transient elevations in hepatic transaminase levels were a notable finding associated with A+P (*5*). However, early onset (day 3–7) and rapid resolution of the transaminase elevations appear consistent with a direct, low-level toxicity. The risk of progressive liver injury with a 3-day course of treatment is likely to be low.

Artesunate + pyronaridine has been administered to patients who have had repeated episodes of malaria, and tolerability on repeat dosing (at intervals as short as 28 days) has been shown to be similar to that on first administration. Where transient elevations in alanine aminotransferase occurred, the adverse event profile was similar with repeat administration for both adults and children (*11*).

Overall, changes in liver function tests due to drug-induced liver injury were mainly mild, with a small number of moderate cases (based on peak total bilirubin levels); the criteria were those of the Drug-Induced Liver Injury Network (*12*). No cases of liver failure or encephalopathy were observed. There was no evidence of coagulopathy or of a delayed effect.

Additional evidence (not in the application)

Data for A+P from six randomized controlled trials enrolling 3718 children and adults were included in a Cochrane systematic review (*13*). In two multicentre trials, enrolling mainly older children and adults from west and south-central Africa, there were fewer than 5% PCR-adjusted treatment failures at 42 days with both A+P and A+L, with no differences between groups (1472 participants, low-quality evidence). Fewer new infections at 28 days were observed in patients given A+P (risk ratio (RR) 0.60; 95% CI 0.40–0.90; 1720 participants; moderate-quality evidence), but no difference was detected at 42 days (1691 participants; moderate-quality evidence).

In one multicentre trial, enrolling mainly older children and adults from south-east Asia, PCR-adjusted treatment failures were 6% by day 42 for A+P and 4% for AS+MQ (RR 1.64; 95% CI 0.89–3.00; 1116 participants; low-quality evidence). Fewer new infections at 28 days were observed in patients given A+P (RR 0.35; 95% CI 0.17–0.73; 1720 participants;

moderate-quality evidence), but no differences were detected at 42 days (1146 participants; low-quality evidence).

This review found serious adverse events to be uncommon in the trials, with no difference detected between treatments.

The analysis of liver function tests showed biochemical elevations were four times more frequent with A+P than with the other antimalarial treatment (RR 4.17; 95% CI 1.38–12.62; four trials; 3523 participants; moderate-quality evidence).

WHO guidelines

The 2015 WHO Guidelines for the treatment of malaria do not currently recommend A+P for general use (conditional recommendation) (*14*).

The Guidelines Development Group considered that the data for A+P, based on the Cochrane systematic review (13) were promising, but that a recommendation for general use was not possible at the time. The Group noted that:

- A+P may be as effective as A+L and AS+MQ in adults and older children.
- Current evidence for young children (under 5 years) is insufficient to conclude that A+P is as effective as alternative treatments.
- Elevations in liver function tests occurred four times more frequently with A+P as with alternative treatments.
- The overall quality of evidence for the critical outcomes was moderate.

Costs/Cost–effectiveness

Costs excluding delivery, cargo insurance and tax from country of origin in public sectors:

Tablet (A+P): 60 mg + 180 mg; US$ 0.60–2.40 per treatment, according to weight band

Granule (A+P): 20 mg + 60 mg; US$ 0.44–1.33 per treatment, according to body weight

Tablet (A+L): US$ 1.34–1.58 per treatment, according to body weight

Tablet (AS+MQ): US$ 0.46–0.76 per treatment, according to body weight.

Availability

A+P tablets and granules are included on WHO's list of prequalified medicines following a positive opinion under Article 58 by the European Medicines Agency. Both tablets and granules are undergoing national approvals in malaria-endemic countries, and some African and Asian countries have already approved the product.

Other considerations

N/A

Committee recommendations

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.

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Artesunate – change: new strength - EMLc

Artesunate **ATC Code: P01BE03**

Proposal

The application requested addition of a new strength (100 mg) of artesunate rectal dose form to the core list of the EMLc for pre-referral treatment of severe malaria in children.

Applicant(s)

Cipla Limited

WHO technical department

WHO Global Malaria Programme

EML/EMLc

EMLc

Section

6.5.3.1 For curative treatment

Dose form(s) and strength(s)

Rectal dose form: 100 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Artesunate rectal dosage form in 50-mg and 200-mg strengths has been included on the EMLc since 2007. Listing includes the same restriction on use for pre-referral treatment of severe malaria only as is requested in the current application.

This additional strength of 100 mg rectal artesunate can offer better compliance in children weighing 5 to <14 kg.

Public health relevance (burden of disease)

In 2015, there were an estimated 214 million new cases of malaria globally, with 438 000 deaths due to the disease, including an estimated 306 000 malaria deaths in children under 5 years of age. The vast majority of cases occurred in the African and south-east Asian regions (*1*).

Mortality approaches 100% in untreated severe malaria but falls to 10–20% with prompt treatment and supportive care. The risk for death from severe malaria is greatest in the first 24 hours: in most endemic countries, transit times between referral and presentation at health facilities are usually long and initiation of treatment is delayed. Pre-referral treatment is recommended, particularly in young children (unless the referral time is less than 6 hours) (*2*).

Summary of evidence – benefits (from the application)

Evidence for the clinical effectiveness of rectal artesunate was evaluated at the time of listing. The application presented the results of two randomized clinical trials in support of the benefits of rectally administered artesunate.

In one trial, 12 068 patients with suspected malaria who could not be treated orally were randomized to receive a single artesunate or placebo suppository. All patients were then referred to facilities where injections could be administered. For the primary end-points of mortality (assessed 7–30 days later) and permanent disability, pre-referral rectal artesunate was associated with a significantly reduced risk of death or permanent disability compared with placebo (1.9% versus 3.8%; risk ratio (RR) 0.49; 95% confidence interval (CI) 0.32–0.77; $P = 0.0013$) in the group of patients who did not reach treatment facilities in less than 6 hours. In patients who did reach facilities within 6 hours, there was no significant reduction in mortality (*3*).

A second trial compared the efficacy of artesunate suppositories and IM artemether in paediatric malaria patients aged 1–10 years. Seventy-nine children were randomized to receive a combination of one or two 50-mg and/or 200-mg thermostable artesunate suppositories to a total dose of 8–17 mg/kg or IM artemether at a dose of 3.2 mg/kg. Compared with the artemether-treated children, those receiving artesunate suppositories had a significantly shorter mean time to 50% parasite clearance (PCT50) (9.1 versus 13.8 hours; $P = 0.008$) and mean time to 90% parasite clearance (PCT90) (15.6 vs 20.4 hours; $P = 0.011$) (*4*).

The application also presented the results of a study of the use, efficacy and parental perception of rectal suppositories in the management of childhood malaria. Rectal artesunate at a dose of 5–10 mg/kg was given to 264 children. After 24 hours, no parasite cells were observed in blood samples of 74% of study participants. Acceptability among parents was high (*5*).

Summary of evidence – harms (from the application)

Evidence for the safety of rectal artesunate was evaluated at the time of listing.

The application presented results of hospital- and community-based studies involving single-dose artesunate suppositories in relation to harms (*6, 7*). Refer to the application for a summary of adverse events and treatment-observed sequelae associated with rectal artesunate.

Additional evidence (not in the application)

N/A

WHO guidelines

WHO's 2015 *Guidelines for the treatment of malaria* (*2*) makes the following recommendations in relation to rectal artesunate as a pre-referral treatment option:

"Where intramuscular injection of artesunate is not available, treat children <6 years with a single rectal dose (10 mg/kg body weight) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults. (Strong recommendation, moderate-quality evidence)."

Costs/Cost–effectiveness

The unit price for artesunate suppositories 100 mg averages US$ 0.33.

Availability

Artesunate 100 mg rectal dose form has been submitted for WHO prequalification. The formulation is manufactured by Cipla Ltd, India.

Other considerations

N/A

Committee recommendations

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.

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Dihydroartemisinin + piperaquine – addition – EML and EMLc

Dihydroartemisinin* + piperaquine phosphate (* also known as artenimol (INN)) ATC Code: P01BF05

Proposal

The application requested addition of a fixed-dose combination formulation of dihydroartemisinin (DHA) + piperaquine phosphate (PQP) to the core list of EML and EMLc as an artemisinin-combination treatment option for the first line treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants.

Applicant(s)

Sigma-Tau, Rome, Italy

WHO technical department

WHO Global Malaria Programme

EML/EMLc

EML and EMLc

Section

6.5.3.1 For curative treatment

Dose form(s) and strength(s)

Tablet: 20 mg + 160 mg; 40 mg + 320 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Currently, the fixed-dose combination (FDC) artemisinin-combination treatments (ACTs) included in the EML are: artemether + lumefantrine (A+L), artesunate + amodiaquine (AS+AQ) and artesunate + mefloquine (AS+MQ).

Public health relevance (burden of disease)

It is estimated that a cumulative 1.2 billion fewer malaria cases and 6.2 million fewer malaria deaths occurred globally between 2001 and 2015 than would have occurred if had incidence and mortality rates remained unchanged since 2000. Of the estimated 6.2

million fewer deaths, about 5.9 million (95%) were in children aged under 5 years.

By 2015, it was estimated that the number of malaria cases had fallen to 214 million (range 149–303 million), and the number of deaths to 438 000 (range 236 000–635 000).

The global burden of mortality is dominated by countries in sub-Saharan Africa. Decreases in case incidence and mortality rates were slowest in countries with the largest numbers of malaria cases and deaths in 2000 (*1*).

Summary of evidence – benefits (from the application)

The application presented the results two phase III clinical trials in adults and children with acute, uncomplicated *P. falciparum* malaria in Africa and south-east Asia.

The Asian trial (*2*) was a randomized, active-controlled, non-inferiority trial to demonstrate the non-inferiority of DHA+PQP, in terms of efficacy, versus AS+MQ (the standard reference therapy in south-east Asia) in 1150 adult and paediatric patients aged between 6 months and 62 years. The primary efficacy end-point was the polymerase chain reaction (PCR)-corrected cure rate at day 63.

At day 63, PCR-corrected cure rates for DHA+PQP versus AS+MQ were 87.9% and 86.6% (intention-to-treat (ITT) population; $P = 0.544$); 97.0% and 95.3% (modified-ITT population (m-ITT); $P = 0.161$); and 98.7% and 97.0% (per-protocol (PP) population; $P = 0.074$), demonstrating similar efficacy for both treatments. For all populations studied, the lower limit of the one-sided 97.5% confidence interval (CI) of the difference was above the prespecified non-inferiority margin of –5%, showing DHA+PQP to be non-inferior to AS+MQ.

In addition, analysis of the 63 days of follow-up showed that DHA+PQP significantly reduced the risk of new infections; Kaplan-Meier estimates of the proportions of patients with new infections were 22.7% for DHA+PQP and 30.3% for AS+MQ, ($P = 0.0042$; ITT population).

The African trial (*3*) had the same design as the Asian trial and investigated the efficacy and safety of DHA+PQP against A+L (the standard reference therapy in Africa) in 1553 paediatric patients aged 6 months to 5 years and weighing at least 5 kg. The primary efficacy end-point was PCR-corrected cure rate at day 28.

At day 28, PCR-corrected cure rates for DHA+PQP versus A+L were 90.4% and 90.0% (ITT population; $P = 0.820$); 92.7% and 94.8% (m-ITT population; $P = 0.128$); and 95.7% for both groups in the PP population ($P = 0.988$). The study demonstrated that the two ACTs were of similar efficacy in curing uncomplicated *P. falciparum* malaria. The lower limit of the one-sided 97.5% CI of the difference was above the non-inferiority margin of –5%, supporting non-inferiority for all populations.

In addition, analysis at 42 days of follow-up showed that DHA+PQP significantly reduced the risk of new infections; Kaplan-Meier estimates of the proportions of patients with new infections were 13.6% (95% CI 11.35–15.76%) for DHA+PQP and 24.0% (95% CI 20.11–27.88%) for A+L ($P < 0.0001$; ITT population).

Similar results have been obtained with DHA+PQP in two pharmacokinetics trials and in other clinical studies reported in literature and summarized in the application (*4–10*).

Summary of evidence – harms (from the application)

In the Asian study (*2*), the proportion of patients experiencing at least one treatment-emergent adverse event (TEAE) was slightly lower in the DHA+PQP group (69.4%) than in the AS+MQ group (72.4%); the difference was not statistically significant. The most frequently reported TEAEs (related and unrelated) in the DHA+PQP and AS+MQ groups, respectively, were headache (18.0% vs 20.2%; $P = 0.364$), malaria (14.5% vs 22.6%; $P = 0.001$), *P. falciparum* malaria (13.4% vs 15.2%; $P = 0.409$) and pyrexia (10.6% vs 11.3%; $P = 0.769$). There were 12 serious TEAEs (1.6%) in the DHA+PQP group and three (0.8%) in the AS+MQ group, including one case of encephalitis that was probably related to MQ. Mild QTc interval prolongation was reported as a TEAE in 5.6% of the DHA+PQP group vs 3.2% of the AS+MQ group. The change in QTc from baseline to day 2 between treatments was statistically significant; by day 7, the QT prolongation was completely resolved.

In the African study (*3*), the proportion of patients experiencing at least one TEAE was similar in the two treatment groups – 79.3% (DHA+PQP) vs 80.6% (A+L); $P = 0.550$. Serious TEAEs were similar in the two groups – 1.7% (DHA+PQP) vs 1.0% (A+L) ($P = 0.249$), respectively, as were the related STEAEs – 1.5% (DHA+PQP) vs 0.8% (A+L) ($P = 0.332$). Mild QTc prolongation was reported as a TEAE in 2.5% of DHA+PQP-treated and 2.6% of A+L-treated patients. No arrhythmias were reported during the study.

A study designed to investigate further the QTc interval effects of DHA+PQP observed in the phase III studies showed that the QTc prolongation observed at the end of the treatment with DHA+PQP administered with a high- or low-calorie diet is significantly reduced when the drug is given with water in fasting conditions (*11*). The Summary of Product Characteristics were consequently modified to state that DHA+PQP should be administered with water and without food.

The safety and efficacy of DHA+PQP in children aged less than 6 months or weighing less than 5 kg have not yet been evaluated.

Additional evidence (not in the application)

A randomized trial compared the efficacy and safety of four artemisinin-based treatments for malaria in 3428 women in the second or third trimester of pregnancy (*7*). DHA+PQP demonstrated the best efficacy, with an overall PCR-adjusted cure rate at day 63 of 99.2% (95% CI 98.2–99.6) vs 94.8%, 98.5% and 96.8% for A+L, AS+AQ and AS+MQ, respectively. The safety profile of DHA+PQP was acceptable, and fewer adverse events were reported in the DHA+PQP group than in the AS+AQ andAS+MQ groups.

WHO guidelines

The 2015 WHO *Guidelines for the treatment of malaria* (*12*) recommend DHA+PQP as an ACT option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide (strong recommendation, high-quality evidence).

The guidelines also recommend use of ACTs to treat uncomplicated *P. falciparum* in pregnant women in the second and third trimesters. Due to limited data on the safety of artemisinin derivatives in early pregnancy, quinine + clindamycin is recommended in the first trimester.

Costs/Cost–effectiveness

Ex-factory prices for DHA+PQP (40 mg + 320 mg, pack of 12 tablets) range from €28.56 to €41.59 in countries of the European Union (EU).

Average ex-factory prices of DHA+PQP (40 mg + 320 mg, pack of 9 tablets) commercialized in 12 African countries range from €2.74 to €3.42.

Median supplier price for A+L (20 mg + 120 mg) is reported as US$ 0.1703 per tablet/capsule (treatment course of 24 tablets/capsules for adults).

The application claims that the greater effect of DHA+PQP in protecting against reinfection compared to artemether+lumefantrine will yield significant cost effectiveness benefits.

Availability

On 9 October 2015, DHA+PQP, manufactured by Sigma-Tau, Italy, achieved WHO prequalification status.

DHA+PQP is marketed in some African, Asian and EU countries. In addition, the product has been sold through governmental agencies and non-profit organizations.

Other considerations

The inclusion of DHA+PQP combination in the EML for the first-line treatment of uncomplicated *P. falciparum* malaria will facilitate its inclusion in the national malaria guidelines of African and other endemic countries.

Committee recommendations

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.

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Section 8: Antineoplastics and immunosuppressives

8.2: Cytotoxic and adjuvant medicines

Erlotinib, gefitinib, afatinib, crizotinib – rejection - EML

Erlotinib	**ATC Code: L01XE03**
Gefitinib	**ATC Code: L01XE02**
Afatinib	**ATC Code: L01XE13**
Crizotinib	**ATC Code: L01XE16**

Proposal

The application requested addition of the tyrosine kinase inhibitor erlotinib to the Complementary List of the EML, with a square box as the representative of the pharmaceutical class, with gefitinib and afatinib available as alternatives, for the treatment of non-small cell lung cancer (NSCLC) in patients with activating mutations of epidermal growth factor receptor.

The application also requested addition of the anaplastic lymphoma kinase (ALK) inhibitor crizotinib to the Complementary List of the EML as first-line treatment for NSCLC in patients with ALK gene rearrangements.

Applicant(s)

Union for International Cancer Control (UICC)

WHO technical department

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

EML/EMLc

EML

Section

8.2 Cytotoxic and adjuvant medicines

Dose form(s) and strength(s)

Erlotinib, tablets: 25 mg, 100 mg, 150 mg

Gefitinib, tablets: 250 mg

Afatinib, tablets: 20 mg, 30 mg, 40 mg

Crizotinib, capsules: 200 mg, 250 mg

Core/Complementary

Complementary

Individual/Square box listing

Square box listing for erlotinib as representative of the class of tyrosine kinase inhibitors (TKIs), with therapeutic alternatives limited to gefitinib and afatinib.

Individual listing for crizotinib.

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

A comprehensive review of NSCLC medicines was conducted in 2015. The Expert Committee endorsed etoposide, carboplatin and paclitaxel (already included on the Complementary List) and recommended the addition of vinorelbine, gemcitabine and cisplatin to the Complementary List for this indication.

At that time, the Committee did not recommend addition of the TKIs gefitinib and erlotinib to the Complementary List, acknowledging that, while individual patients with a drug-sensitive epidermal growth factor receptor (EGFR) mutation may derive a substantial extension of life, the average increase in progression-free survival was modest (3–4 months).

The Committee also considered that substantial infrastructure would be required to establish routine and reliable molecular testing for EGFR mutations in NSCLC. The Committee considered it was neither practical nor cost effective to establish molecular testing, and the use of TKIs as essential medicines for this disease could therefore not be supported.

Afatinib and crizotinib were not proposed for inclusion by applicants nor recommended by the Expert Committee.

Public health relevance (burden of disease)

According to GLOBOCAN, lung cancer has been the most common cancer globally for several decades; estimated worldwide incidence in 2012 was 23.1 per 100 000 (age-standardized rate (ASR)) (12.9% of all cancers) (*1*). Of the 1.8 million new cases in 2012, 58% occurred in less-developed regions; ASR incidence rates were highest in central and eastern Europe (53.5 per 100 000) and in eastern Asia (50.4 per 100 000) and were 25% higher for men than for women (205 and 165 per 100 000 respectively). GLOBOCAN estimated the global mortality ASR in 2012 to be 19.7 per 100 000. Lung cancer had the second highest absolute incidence globally after breast cancer, and was the leading cause of death from malignant disease in 93 countries, accounting for one fifth of the total global burden of disability-adjusted life years from cancer.

The most common form of the disease is NSCLC, which accounts for 85–90% of all lung cancers (*2, 3*).

Most patients with NSCLC present with advanced stage disease – stage IV in particular – and half of all patients treated initially for potentially curable early-stage disease will experience recurrences with metastatic disease (*4*). Patients with stage IV disease are never curable, and chemotherapy, targeted therapy and radiation can only extend survival and palliate symptoms. Although NSCLC is generally regarded as a disease of the elderly, a third of cases are diagnosed in patients under 65 years of age (*4*). Platinum-based doublet chemotherapy is the standard first-line treatment for patients with advanced (stage IV) disease.

Summary of evidence – benefits (from the application)

Where high-quality molecular diagnostics and targeted therapies are available, patients with activating mutations of EGFR may benefit from treatment with TKIs (erlotinib, gefitinib and afatinib).

EGFR-sensitizing mutations (defined as in-frame deletions in exon 19 and L858R substitution in exon 21), are found in 10% of Caucasians with NSCLC and up to 50% of Asian patients (*5*). ALK gene rearrangements are found in 3–7% of NSCLC (*6–9*). The incidence of mutation rates is still unknown in most parts of the world.

Patients with driver oncogenes who have not previously received a targeted therapy may be treated with EGFR-TKIs or crizotinib as salvage therapy (*10*).

The application did not summarize the evidence and conclusions were not supported by a valid review process. For this reason, evidence has been complemented by the Secretariat.

Erlotinib, gefitinib, afatinib

A Cochrane systematic review assessed the effectiveness of single-agent or combination EGFR therapies used in the first-line treatment of people with locally advanced or metastatic EGFR mutation-positive NSCLC compared with other cytotoxic chemotherapy agents, used alone or in combination, or best supportive care (*11*).

Nineteen trials were included, involving 2317 patients, of whom 1700 were of Asian origin.

The review reports that "overall survival (OS) data showed inconsistent results between the included trials that compared EGFR-targeted treatments against cytotoxic chemotherapy or placebo".

When erlotinib was compared with platinum-based chemotherapy, the overall treatment effect indicated no significant difference in OS between the groups, with a hazard ratio (HR) of 0.95 (3 studies; 95% confidence interval (CI) 0.75–1.22). For progression-free survival (PFS), however, erlotinib showed a statistically significant benefit compared with cytotoxic chemotherapy (4 studies; HR 0.30; 95% CI 0.24–0.38).

One small trial (FASTACT 2) did report statistically significant OS (HR 0.48; 95% CI 0.27–0.85) and PFS (HR 0.25; 95% CI 0.16–0.39) gains for participants treated with erlotinib plus cytotoxic chemotherapy compared with cytotoxic chemotherapy alone, while another trial showed no meaningful differences between erlotinib and vinorelbine (OS HR 2.16; 95% CI 0.58–8.10).

It was not possible to combine all single estimates of the effect sizes in an overall estimate.

Four trials compared gefitinib with platinum-based chemotherapy. Trial results did not show statistical differences for OS (1 trial, gefitinib vs gemcitabine plus cisplatin: HR 1.04, 95% CI 0.50–2.20; gefitinib vs carboplatin and paclitaxel: two trials, HR 0.95, 95% CI 0.77–1.18; gefitinib vs docetaxel plus cisplatin: one trial, HR 1.25, 95% CI 0.88–1.78).

Four studies provided data for PFS. Trials showed statistically significant differences in time before the cancer progressed between gefitinib and platinum-based chemotherapy, to a large extent in some cases (gefitinib vs gemcitabine plus cisplatin: HR 0.54, 95% CI 0.27–1.10; gefitinib vs paclitaxel plus carboplatin: two trials, HR 0.39, 95% CI 0.32–0.48; gefitinib vs docetaxel plus cisplatin: one trial, HR 0.49, 95% CI 0.34–0.71).

When gefitinib was added to platinum-based chemotherapy and compared with platinum-based chemotherapy (two studies), results were not significantly different for either OS (HR 1.77 95% CI 0.50–6.23) or PFS (HR 0.55; 95% CI 0.19–1.60).

Afatinib (*n* = 709) showed a statistically significant PFS benefit when compared with chemotherapy in a pooled analysis of two trials (HR 0.42; 95% CI 0.34–0.53). Results for OS were immature.

Indirect comparisons showed that the three EGFR-TKIs have similar efficacy but may differ within class in terms of toxicities (*12, 13*). However, indirect comparisons might not be appropriate because of the different enrolled populations across the included trials.

Crizotinib

For patients with ALK gene rearrangements, second-line crizotinib has been associated with improvements in PFS when compared with pemetrexed or docetaxel (7.7 months in the crizotinib group and 3.0 months in the chemotherapy group: HR 0.49; 95% CI 0.37–0.64). However, OS showed no significant improvement with crizotinib compared with chemotherapy (HR 1.02; 95% CI 0.68–1.54; *P* = 0.54) (*14*).

Among patients givenIn crizotinib for first-line treatment, compared with pemetrexed in combination with cisplatin or carboplatin, there was a significantly longer PFS (median 10.9 months vs 7.0 months; HR 0.45; 95% CI 0.35–0.60) but no significant improvement in OS (median overall survival was not reached in either group; HR, 0.82; 95% CI 0.54–1.26) (*15*).

Data are still too immature to allow firm conclusions to be reached. Selective cross-over from the control arm to the intervention arm might dilute the benefits associated with crizotinib, making inferences about effectiveness difficult, even when the total number of events required for the final analysis of OS is reached.

Evidence from one observational study (*10*) showed that crizotinib was associated with improvement in OS compared with chemotherapy: 1-year OS was 70% (95% CI 50–83%) for the crizotinib-treated group versus 44% (95% CI 23–64%) for the crizotinib-naive group; 2-year OS was 55% (95% CI 33–72%) versus 12% (95% CI 2–30%) (HR 0·36; 95% CI 0.17–0.75). This was a small study and should be interpreted with caution. More than a third of the crizotinib group had received multiple lines of therapy, suggesting a potentially more indolent disease course. Nearly a third of the control patients were screened for ALK with the intention of enrolling in a trial but were subsequently deemed ineligible. Patient selection and indication biases could therefore have contributed to a systematic imbalance that favoured improved survival in the crizotinib group and worse survival in the control group.

Summary of evidence – harms (from the application)

Both EGFR-TKIs and the ALK inhibitor are well tolerated by many patients. Agents have similar toxicity profiles, although the incidence of toxicity depends on the drug. Diarrhoea and skin rash are the most common grade 3 and 4 adverse events, but their incidence is highly variable (*11*). Rarely, more severe gastrointestinal toxicity, including perforation, can occur, particularly with erlotinib (*16*). All agents may also cause hepatic toxicity and increased hepatic transaminases. Hepatic failure and hepatorenal syndrome have been

reported in patients treated with erlotinib, although the incidence is low.

The common side-effects of crizotinib are diarrhoea, oedema, vision changes and elevation in aminotransferase levels.

Cytotoxic chemotherapy was associated with greater grade 3/4 myelosuppression, fatigue and anorexia.

Additional evidence (not in the application)

See benefits and harms sections.

WHO guidelines

N/A

Costs/Cost–effectiveness

The contributors to the applications suggested that price adjustments are imminent that will make the cost of the three TKIs comparable in the near future. However, no data were provided on costs, cost comparisons or cost analyses.

EGFR-TKIs and the ALK inhibitor are more expensive than standard chemotherapies. However, as they are oral medicines, administration is simple compared with that of, for example, docetaxel, which should be administered in a specialized health care unit.

Availability

No information provided in the application.

Other considerations

N/A

Committee recommendations

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.

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Nilotinib, dasatinib – addition – EML

Nilotinib **ATC Code: L01XE08**
Dasatinib **ATC Code: L01XE06**

Proposal

The application requested addition of nilotinib and dasatinib to the Complementary List of the EML and EMLc as second-line therapy for the treatment of patients with chronic myeloid leukaemia and intolerance of or haematological resistance to imatinib.

Applicant(s)

Union for International Cancer Control (UICC)

WHO technical department

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

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EML/EMLc

EML and EMLc

Section

8.2 Cytotoxic and adjuvant medicines

Dose form(s) and strength(s)

Nilotinib, capsules: 150 mg, 200 mg

Dasatinib, tablets: 20 mg, 50 mg, 80 mg, 140 mg

Core/Complementary

Complementary

Individual/Square box listing

Square box listing of nilotinib, with alternatives limited to dasatinib.

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

A comprehensive review of medicines for chronic myeloid leukaemia (CML) was done in 2015. Imatinib was added to the EML. For nilotinib and dasatinib, the Expert Committee considered the evidence presented for the second-line setting was insufficient to warrant a positive recommendation.

Public health relevance (burden of disease)

According to GLOBOCAN, estimated worldwide total leukaemia incidence for 2012 was 351

965, with an age-standardized rate (ASR) of 4.7 per 100 000 per year, a 5-year prevalence of 1.5% and a male:female ratio of approximately 1:4. Leukaemia incidence in more developed regions in 2012 was estimated at 7.2 per 100 000 (ASR) compared with 3.8 per 100 000 in less developed regions (*1*). GLOBOCAN provides no specific information about CML.

Information on CML incidence and prevalence is scarce as the disease is rare. A European study published in 2007 estimated annual incidence to be 1 or 2 cases per 100 000 people (*2*). The same study stated that CML is most common in older populations, with a median age at diagnosis of around 65 years, and more common in men (although women tend to have a higher survival rate). Disease incidence appears to be consistent across geography and ethnicity, although it is noted that survival rates in some countries are likely to be impacted by the availability of drugs and diagnostic technologies. In USA, for instance, rates for new CML cases have been stable over the past 20 years, but death rates have dropped significantly, with 5-year relative survival rising from about 30% to 63% (*3*).

Summary of evidence – benefits (from the application)

Approximately one fifth of patients are intolerant of imatinib and will discontinue therapy. The Unmet Needs in CML (UNIC) study, a cross-sectional study with retrospective chart review of patients treated for CML across eight European countries, estimated the proportion of imatinib-treated patients who experienced imatinib resistance and/or intolerance (*4, 5*). A total of 20–23% of patients stopped – and did not restart – imatinib during the study period.

In addition, five years or more after achievement of complete cytogenetic remission, therapeutic effects of imatinib will be unsatisfactory in about one third of patients; recurrent disease will then develop (*6, 7*).

Second-generation tyrosine kinase inhibitors (TKIs) – nilotinib and dasatinib – have been proposed as second-line therapies in view of their potency and activity against mutated forms of the *BCR–ABL1* gene.

The application reported that approximately 50% of patients who are resistant to imatinib will achieve a complete cytogenetic remission when treated with either nilotinib or dasatinib (*8, 9*); responses are durable in about 80% of patients.

In a phase I dose-escalation study evaluating the safety and efficacy of nilotinib in chronic-phase CML, 92% of patients with resistance or intolerance to imatinib achieved a complete haematological response following treatment with nilotinib (*10*). A phase II open-label study investigated the effectiveness of nilotinib, 400 mg twice daily, in 321 patients with chronic-phase CML who had failed or were intolerant to imatinib (*9*). All patients were followed for more than 24 months. The rate of major cytogenetic response was 59%. Forty-four percent of the patients who achieved a major cytogenetic response attained a complete response. Estimated survival at 12 months was 87%.

Dasatinib was studied in imatinib-resistant or -intolerant patients with CML in a phase I dose-escalation study (*11*). The rates of complete haematological response and major cytogenetic response in the 40 patients with chronic-phase CML were 92% and 45%, respectively. Efficacy of dasatinib, 70 mg twice daily, has also been demonstrated in the myeloid or lymphoid blast phase in phase II trials (*8, 12*). After at least 12 months' follow-

up in one study (*12*), major cytogenetic responses were achieved in 33% and 52% of patients respectively. A complete cytogenetic response was achieved in 26% of myeloid blast-phase patients and 46% of lymphoid blast-phase patients. Median progression-free survival was 6.7 months and 3.0 months in myeloid blast-phase and lymphoid blast-phase patients, respectively; median overall survival was 11.8 months and 5.3 months.

A systematic review and network meta-analysis assessed the efficacy of imatinib, dasatinib and nilotinib in newly diagnosed chronic myeloid leukaemia (*13*). Eight randomized controlled trials (RCTs; 3520 participants) were included. At 18 months, compared with imatinib 400 mg (40.1%, reference category), the probability of a complete cytogenetic response was greater, and statistically significant, for dasatinib 100 mg (79.1%; 95% credibility interval (CrI) 72.0–85.1%), nilotinib 600 mg (83.1%; 95% CrI 76.7–88.4%), and nilotinib 800 mg (80.0%; 95% CrI 73.0–85.5%). However, imatininb at 800 mg daily was associated with substantial benefits in terms of complete cytogenetic response, similar to those with dasatininb and nilotinib (77.9%; 95% CrI 71.9–83.2%). In indirect comparisons with each other, dasatinib and nilotinib showed similar efficacy. Evidence is weak and limited as findings are based on comparisons of only one or two RCTs, with high uncertainty. Other clinically relevant outcomes, such as survival, were not explored.

A second systematic review showed both dasatinib and nilotinib to be associated with a statistically significant advantage compared with imatinib in terms of complete cytogenetic and major molecular response as first-line option (14). Again, data were based on immature surrogate outcomes, assumptions of life expectancy and extreme uncertainty.

Summary of evidence – harms (from the application)

Tyrosine kinase inhibitors are well tolerated by most patients. The most common non-haematological adverse reactions are oedema, muscle cramps and gastrointestinal symptoms, including nausea, vomiting, diarrhoea and abdominal pain; most adverse effects are mild (*15, 16*).

Dasatinib is associated with gastrointestinal bleeding in up to 25% of patients; however, the bleeding is typically mild to moderate and resolves given a drug holiday. Patients treated with dasatinib may also experience pulmonary complications, including pleural effusions which can be grade 3–4 in up to 10% of patients (*17*).

Nilotinib and dasatinib are associated with QT prolongation (*16*). Nilotinib is also associated with peripheral vascular disease and atherosclerosis-related events; however, the incidence of this adverse effect is low (<5%) although it may be higher with longer follow-up (*18*).

Additional evidence (not in the application)

N/A

WHO guidelines

N/A

Costs/Cost–effectiveness

The second systematic review also provided economic analyses (*14*). In the first-line treatment setting and assuming cost–effectiveness based on a willingness-to-pay decision threshold of £20 000 – £30 000 per quality-adjusted life year, nilotinib was found to be cost effective compared with imatinib, while dasatinib was not.

No information was presented in the current application regarding the cost–effectiveness of second-line TKI treatment.

Availability

Second generation TKIs are effective only in patients whose leukaemia cells carry the *t*(9;22) chromosomal translocation, and identification of the translocation is therefore critical before a decision is made to use imatinib therapy and thus TKI therapy. Although more than 90% of CML cases do indeed demonstrate this translocation, CML can be confused with other myeloproliferative diseases that do not. Testing can be performed by a variety of molecular techniques; it is routinely available in most cancer centres in the developed world but often unavailable in laboratories in developing countries. Where it is unavailable, it is possible for centres to partner with referral laboratories to have testing performed. Newer technology is rapidly making tests more generally available in developing countries (*19, 20*).

Other considerations

N/A

Committee recommendations

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.

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Trastuzumab emtansine – rejection – EML

Trastuzumab emtansine (T -DM1) **ATC Code: L01XC14**

Proposal

The application requested the addition of trastuzumab emtansine to the Complementary List of the EML as second-line therapy for the treatment of locally advanced or metastatic breast cancer, after trastuzumab therapy failure.

Applicant(s)

Knowledge Ecology International (KEI)

WHO technical department

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

EML/EMLc

EML

Section

8.2 Cytotoxic and adjuvant medicines

Dose form(s) and strength(s)

Powder for injection: 100 mg; 160 mg in vial

Core/Complementary

Complementary

Individual/Square box listing

Individual

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

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate (ADC) consisting of the monoclonal antibody trastuzumab (T) covalently bonded via a synthetic linker, succinimidyl *trans*-4-(maleimidylmethyl)cyclohexane-1-carboxylate (SMCC), to the cytotoxic agent emtansine (DM1), a maitansine derivative (*1*).

T-DM1 had not previously been considered by the Expert Committee, while trastuzumab has been considered and included in the EML in 2015 for treatment of early-stage and metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer (*2*).

The trastuzumab moiety is a humanized anti-HER2 antibody that seeks out cells that overexpress HER2. Trastuzumab exhibits anti-tumour activity by inhibiting angiogenesis

and recruiting natural killer (NK) cells through antibody-dependent cell-mediated cytotoxicity (*3*). On binding to the receptor, the antibody moiety also induces an anti-proliferative effect by down-modulating HER2 growth signalling pathways (*4*).

In addition, T-DM1 delivers the cytotoxic DM1 payload to target cells. When T-DM1 selectively binds to the HER2 receptor, it is internalized via endocytosis and undergoes lysosomal proteolytic degradation, slowly releasing linker-bound DM1 into the cell. DM1 is a highly toxic antimitotic agent that disrupts microtubule assembly. Once released, however, the linker – still covalently bonded to DM1 – prevents it from crossing the plasma membrane, so keeping levels in blood plasma initially low.

Thus, T-DM1 has important innovative chemical properties: SMCC keeps the ADC stable in the extracellular environment and, once in the cells, prevents the cytotoxic part from being released back into extracellular space that would cause damage to healthy cells (*5*).

Public health relevance (burden of disease)

Cancer is the second leading cause of mortality worldwide, responsible for 8.2 million deaths globally, and with an incidence of 14.9 million in 2013 (*6*). More than 60% of global cancer cases occur in Africa, Central and South America, and Asia; these regions generally experience a higher mortality relative to incidence rates as a result of higher proportions of late diagnoses, poor-prognosis cancer, and the scarcity of clinical care (*7*). High-income countries have benefited from screening programmes, networks of clinical centres dedicated exclusively to the diagnosis and treatment of breast cancer, and early adoption of newer generations of neoplastic inhibitors and antibody-based targeted treatments.

Breast cancer is the primary cancer among women and the second most common cause of cancer overall (*7*). Incidence reached 1.8 million in 2013, with mortality and morbidity higher in developing countries (8257.05 thousand disability-adjusted life-years (DALY); 95% confidence interval (CI) 7517.37–8998.96) than in developed countries (4811.57 thousand DALY; 95% CI 3838.96– 5490.48) (*6*).

Breast cancer is a heterogeneous disease whose response can differ based on individual genotype. Up to 25 % of breast cancers are HER2-positive: at least 450 000 women worldwide were newly diagnosed with HER2-positive breast cancer in 2013. Over the past three decades, improved understanding of the molecular mechanisms and phenotypic expression profiles of cancer has allowed scientists to develop highly targeted and effective systemic treatments (*8*).

HER2 is a 185-kDa transmembrane tyrosine kinase receptor encoded by the *ERBB2* oncogene. Its overexpression leads to constitutive activation of mitogen-activated protein kinases (MAPK) and protein kinase B (AKT) signalling pathways, resulting in elevated metabolic function, increased proliferation and enhanced invasiveness of the tumour cells (*9*). The natural history and prognosis of breast cancer cells expressing high levels of HER2 is associated with more aggressive tumours and poor sensitivity to standard chemotherapeutic agents (*10*).

Summary of evidence – benefits (from the application)

Currently, trastuzumab-containing therapies are the preferred first-line treatment for

HER2-positive metastatic breast cancers and a standard part of earlier-stage adjuvant therapy. However, most metastatic breast cancer patients will progress under such therapy within 1–2 years. These patients require newer HER2-directed therapies that are well tolerated in treatment-experienced patients (*11*). Unfortunately, the mechanism behind primary and acquired resistance to trastuzumab (lack of positive response to therapy or disease progression after an initial clinical benefit), remain elusive and most patients will develop resistance (*12–14*).

The Cochrane Library Database of Abstracts of Reviews of Effectiveness was searched for systematic reviews, technology assessment reports and meta-analyses of controlled clinical trials involving T-DM1 in at least one arm. Additional searches for relevant reviews were undertaken in Clinical Evidence (CE), PubMed, and the Cochrane Database of Systematic Reviews. T-DM1 is still a relatively new medical technology and there is a paucity of syntheses of evidence: only two published meta-analyses for T-DM1 treatment in breast cancer were found (*15, 16*). For the purpose of the application, the meta-analysis by Shen et al. (*15*) was retained and supplemented with information from the technology appraisal from the National Institute for Health and Care Excellence (NICE) (*17*). Two notable clinical trials (EMILIA, TH3RESA) examining TDM-1 in treatment-experienced patients with advanced-stage breast cancer were central to the application because of their completion (i.e. they had reached their primary end-points) and statistical power.

Locally advanced and metastatic breast cancer

The pivotal EMILIA study was a phase III, international, open-label, randomized clinical trial (RCT) comparing T-DM1 (3.6 mg/kg every 3 weeks) with lapatinib (1250 mg daily) plus capecitabine (2000 mg/m2) (LC) in women who had unresectable, locally advanced or metastatic HER2- positive breast cancer and who were previously treated with trastuzumab and a taxane (e.g. paclitaxel, docetaxel) (*18*). Between 2009 and December 2011, 991 patients were randomized. Two co-primary outcome measures were progression-free survival (PFS) and overall survival (OS). Patients given T-DM1 exhibited an increase in median OS of 30.9 months compared with 25.1 months for LC-treated patients (hazard ratio (HR) 0.68; 95% CI 0.55–0.85; $P < 0.001$]. PFS, assessed by an independent review, was significantly improved for T-DM1 – 9.6 months compared with 6.4 months for LC (HR 0.65; 95% CI 0.55–0.77; $P < 0.001$). Patient-reported outcomes (PRO), which evaluate the subjective impact of the treatment on the patient's quality of life, were shown to be superior for T-DM1. PRO was measured with the Trial Outcome Index–Physical/Functional/Breast (TOI-PFB) subset of the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire; there was a statistically significant delay in predefined symptom-worsening secondary end-points for T-DM1 compared with LC (7.1 months vs 4.6 months; HR 0.796; 95% CI 0.667–0.951; $P = 0.0121$) (*19*).

The second phase III, open-label, RTC, TH3RESA, aimed to study T-DM1 in more heavily pretreated metastatic breast cancer patients with previous exposure to lapatinib (*20*). TDM-1 (3.6 mg/kg IV, every 21 days) was compared with a treatment of physician's choice (TPC) in patients with advanced or metastatic breast cancer who had progressed after two or more HER2-directed regimens. In the TPC arm, 85% of patients were given trastuzumab plus another agent, 3% lapatinib plus chemotherapy and 17% were treated with single-

agent chemotherapy. Patients (n = 602) were randomized in a 2:1 ratio for T-DM1, and 44 patients who had progressed on TPC crossed over to the T-DM1 arm. Co-primary endpoints included PFS and OS. PFS was significantly greater with TDM-1 (6.2 months vs 3.3 months; HR 0.528; 95% CI 0.422–0.661; P < 0.0001). At the time of the initial (2014) report, OS was still immature. Final OS was presented in December 2015 at the San Antonio Breast Cancer Symposium and showed a significant increase in survival with T-DM1 at 22.7 months compared with 15.8 months for TPC (HR 0.68; P = 0.0007) (*21*).

A 2016 meta-analysis included nine eligible studies, three phase I clinical trials, four phase II and two phase III (*15*). The overall hazard ratios for PFS and OS were calculated by meta-analysing, respectively, three (EMILIA (*18*), TH3RESA (*20*), BO21976 (*22*)) and two (EMILIA, TH3RESA,) controlled trials.

Median PFS significantly favoured T-DM1; difference ranged from 2.9 months to 5 months (total HR 0.60; 95% CI 0.53–0.69). Cumulative OS was associated with an improved survival for T-DM1 compared with TPC (odds ratio (OR) 0.60; 95% CI 0.48–0.75). Heterogeneity was low in both analyses.

The National Institute for Health and Care Excellence (NICE) published its technology appraisal for T-DM1, assessing efficacy and cost–effectiveness (*23, 24, 25*). As part of the process, NICE reviewed evidence submitted by Roche, clinical experts and other stakeholders; clinical evidence came primarily from EMILIA and TH3RESA clinical trials. Because head-to-head treatment comparisons were available only for LC, the company conducted a Bayesian network meta-analysis using a fixed-effect model involving five clinical trials (EMILIA, CEREBEL, EGF100151, NCT00777101 and GBG26). NICE's Evidence Review Group (ERG), reviewing Roche's submission, repeated the network meta-analysis using a random-effects model. From the ERG's model, compared with CL, T-DM1 was associated with a 32% decrease in hazard of death (HR 0.68; 95% credible Interval (CrI) 0.37–1.25) and a 35% reduction in the hazard of tumour progression or death (HR 0.65; 95% CrI 0.35–1.20). However, the authors report that CrI values "do not rule out the possibility that T-DM1 is less efficacious than comparators" (*25*).

Comparison with trastuzumab

Trastuzumab is associated with relevant benefits in HER2-positive breast cancer patients. In a systematic review of eight studies, total 11 991 patients, the combined HRs for OS and disease-free survival (DFS) significantly favoured trastuzumab-containing regimens (HR 0.66; 95% CI 0.57–0.77; P < 0.00001; and HR 0.60; 95% CI 0.50–0.71; P < 0.00001, respectively) (*26*). Currently, a combination of trastuzumab with a taxane is considered to be the standard of care (i.e. first-line) in metastatic breast cancer. The phase 3 randomized controlled clinical trial MARIANNE, not included in the review mentioned above, studied untreated HER2+ metastatic breast cancer patients receiving T-DM1 plus pertuzumab, T-DM1 plus placebo, or a combination of trastuzumab with a taxane (paclitaxel or docetaxel). In an interim analysis, therapies containing T-DM1 were non-inferior to trastuzumab and taxane treatments for PFS. However, OS curves essentially overlapped, and median OS has not been reached in any arm. T-DM1 was better tolerated, contributing to better quality of life secondary end-points and less treatment discontinuation related to adverse events (*27*). The trial is still in progress.

Summary of evidence – harms (from the application)

In the EMILIA trial, safety was better for T-DM1, with decreased rates of serious adverse events (41% for T-DM1, 57% for LC). The most common adverse reaction of grade 3 or higher for T-DM1 was thrombocytopenia, at 12.9% vs 0.2%, and elevated transaminase, at 7.2% vs 2.2% (*18*). In the TH3RESA trial, overall serious adverse events of grade 3 or higher were more common for TPC than for T-DM1. More thrombocytopenia of grade 3 or higher was seen in the T-DM1 arm (6.0% vs 2.7%) (*21*).

In the meta-analysis, the most common adverse events were anaemia, fatigue, increased transaminases, nausea, thrombocytopenia, arthralgia and headache, although severe events (>grade 3) were relatively rare. In controlled studies only, the highest odds ratio associated with T-DM1 was for thrombocytopenia at 8.5 (95% CI 3.96–18.22) for all grades and 7.27 (95% CI 1.10–48.11) for grade 3 or greater. Other significant adverse events were all-grade fatigue (OR 1.29; 95% CI 1.04–1.59) and all-grade increased transaminases at (OR 4.04; 95% CI 1.43–11.43) (*15*).

Additional evidence (not in the application)

Results of the MARIANNE study (mentioned above) were published after closure of the EML application period (*28*). Regimens containing TDM-1 were found to be non-inferior (but not superior) to trastuzumab plus taxane in terms of PFS in patients with previously untreated HER2-positive metastatic breast cancer (i.e. first-line setting), and showed better tolerability. In the first-line treatment setting for metastatic HER2-positive breast cancer, TDM-1 may be a valid treatment option for some patients.

WHO guidelines

N/A

Costs/Cost–effectiveness

After analysing the technology appraisal, NICE concluded that T-DM1 was a clinically effective for treatment for HER2-positive, unresectable, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, but ultimately did not find it to be cost effective at the price that Roche was offering at the time (*24*).

Availability

T-DM1 is sold internationally under the brand name Kadcyla, a product of Genentech/F. Hoffmann-La Roche Ltd, as well as through arrangements with other companies.

T-DM1 is approved for HER2-positive advanced and metastatic breast cancer in adult patients who have previously received trastuzumab and a taxane, separately or in combination in: Australia (Therapeutic Goods Administration), the European Union (European Medicines Agency, EMA), Japan (Pharmaceuticals and Medical Devices Agency and USA (U.S. Food & Drug Administration, FDA).

There are currently no biosimilars of T-DM1 on the market. In November 2016, however, the Coalition for Affordable T-DM1 requested a compulsory licence on T-DM1 patents from

the British government (refer to Attachment 1 of the application).

Roche's Herceptin (trastuzumab), was approved by the FDA in September 1998 and by the EMA in August 2000.

Three biosimilar versions of trastuzumab are commercially available in India and the Islamic Republic of Iran for the treatment of breast cancer, and a fourth in Russia. There are at least four biosimilars in phase III trials. The first biosimilar was developed by Biocon and Mylan and received market authorization in India in 2013. In January 2015, BIOCAD announced the first trastuzumab biosimilar to be approved by the Ministry of Health of the Russian Federation. The Islamic Republic of Iran also approved its own version of the monoclonal antibody in January 2016 and announced its readiness to export the drug to other countries in the Middle East and central Asia when trade sanctions were lifted.

Other considerations

N/A

Committee recommendations

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.

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Zoledronic acid – addition – EML

Zoledronic acid — ATC Code: M05BA08

Proposal

The application requested addition of bisphosphonates to the Complementary List of the EML as a therapy for patients with cancer and bone metastases. The application proposed a square box listing of zoledronic acid, with therapeutic alternatives limited to:

- Breast cancer:
  - pamidronate (ATC: M05BA03)
  - ibandronate oral and IV (ATC: M05BA06)
  - clodronate (ATC: M05BA02)
- Multiple myeloma:
  - pamidronate
  - clodronate

Applicant(s)

Union for International Cancer Control (UICC)

WHO technical department

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

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EML/EMLc

EML

Section

8.2 Cytotoxic and adjuvant medicines

Dose form(s) and strength(s)

Concentrated solution for infusion: 4 mg/5 mL in 5-mL vial

Solution for infusion: 4 mg/100 mL in 100-mL bottle

Core/Complementary

Complementary

Individual/Square box listing

Square box listing for zoledronic acid as representative of the pharmacological class of bisphosphonates.

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

Bisphosphonates have not previously been considered by the Expert Committee for addition to the EML.

Public health relevance (burden of disease)

The skeleton is one of the most common locations to which cancer metastasizes. The propensity for solid tumour malignancies to metastasize to bone varies: bone metastases will develop in 65–75% of patients with advanced prostate cancer and 70% of patients who die of breast cancer. The incidence of bone metastases is lower in patients with lung, colon, stomach, bladder and other cancers (15–30%), and only 5% of patients with certain gastrointestinal malignancies (*1*). In patients with multiple myeloma, 60% of patients will have bone lesions at the time of presentation and nearly all patients will develop bone lesions during the course of the disease (*2*).

Bone metastases can cause skeletal-related events (SREs) including fractures, spinal cord compression, hypercalcaemia and significant pain, which can then necessitate treatment with radiation and/or chemotherapy or surgical intervention in the case of fractures or spinal complications. In patients with bone metastases treated with systemic anticancer regimens and no bisphosphonates, SREs occur in 46–64% of patients within 2 years (depending on the underlying malignancy), contributing importantly to the significant overall morbidity of advanced cancer (*3–5*).

Summary of evidence – benefits (from the application)

Bisphosphonates are specific inhibitors of osteoclasts, and their use in cancer patients prevents the increased bone resorption that accompanies metastatic bone disease (*6, 7*). Through this mechanism, bisphosphonates reduce complications or SREs such as fractures, the need for palliative radiotherapy to relieve pain, spinal cord compression and hypercalcaemia from bone metastases (*8, 9*). They can also reduce bone pain and analgesic requirements (*10, 11*) and improve quality of life (*3, 12, 13*).

In the absence of a bisphosphonate, SREs occur in around one half to two thirds of patients (depending on the underlying malignancy and concomitant cancer treatments) (*3–5*), contributing significant morbidity to the clinical course of the underlying disease and increasing the health care costs of treating advanced malignancy (*8, 14*).

Bisphosphonates reduce the number of breast cancer patients experiencing an SRE, extend the time to first and subsequent SREs, and prevent around a third of all skeletal morbidity (*4, 5, 13, 15*). Zoledronic acid is likely to be the most effective agent (*16–18*), reducing by 41% the overall risk of SREs when compared with placebo (*19*). Placebo-controlled trials have also shown benefits for oral clodronate (*20–22*), IV (*23, 24*) and oral (*24, 25*) ibandronate and pamidronate (*3, 13, 15*) but to a lesser extent than zoledronic acid (*17*).

In hormone-resistant prostate cancer, inhibition of bone resorption is also of clinical relevance despite the osteoblastic nature of most prostate bone metastases (*26, 27*). However, only zoledronic acid has shown significant benefits in terms of reducing SREs (*4, 28*), although IV ibandronate has similar efficacy to palliative radiotherapy for the acute relief of bone pain (*11*). In this disease setting, zoledronic acid reduced the number of

patients experiencing an SRE by 9% (33% vs 44%), increased the median length of time to first SREs (>420 days vs 321 days), reduced the overall risk of SREs by 36% and improved pain scores (*4*).

Similarly, in non-breast and non-prostate solid tumours (50% non-small cell lung cancer and 50% miscellaneous other solid tumours), zoledronic acid increased the median time to the first event (230 days vs 163 days) and reduced the overall risk for SREs by 31% (*4, 29*).

In multiple myeloma (*30*), bisphosphonates reduce vertebral fractures, SREs and bone pain (relative risk of 0.74, 0.80 and 0.75, respectively) with oral clodronate (*31, 32*), pamidronate (*33*) and zoledronic acid (*16, 17*) having similar effects on skeletal morbidity. However, zoledronic acid improved overall survival when compared with oral clodronate and extended survival by 3 months (*34*).

Summary of evidence – harms (from the application)

Several risks are associated with treatment with bisphosphonates and require monitoring (*8, 35*).

Intravenous bisphosphonates are commonly associated with the acute-phase response (fever and influenza-like symptoms), and bone/joint pain. Less common side-effects include kidney injury (*36*), ocular inflammation (*37*) and atrial fibrillation (*38*).

Osteonecrosis of the jaw (ONJ) is a significant clinical problem associated with long-term bisphosphonate use (*39*). The frequency of ONJ is 1–2% of patients for each year on monthly IV bisphosphonate therapy (*40, 41*); the risk may be less with daily oral agents or with a 3-monthly schedule of IV treatment (*42*). It is recommended that patients have a dental examination and preventive dental work (such as tooth extraction) before administration of bisphosphonate therapy; invasive dental work should be avoided (*42*). When extraction or jaw surgery cannot be avoided, prophylactic antibiotics should be given. The bisphosphonate should be discontinued until healing is complete unless the patient has ongoing significant symptomatic bone disease.

Patients are also at risk of hypocalcaemia. Vitamin D supplementation is recommended and most patients should be placed also on calcium supplementation, which should be individualized on the basis of the characteristics of the malignancy and renal function (*43*).

Atypical femoral fractures (subtrochanteric and diaphyseal regions) can also occur rarely (<1 in 1000) and may be related to long-term suppression of bone remodelling induced by bisphosphonate treatments (*44*).

Additional evidence (not in the application)

N/A

WHO guidelines

The WHO *Guidelines for management of cancer pain* are currently under review.

Costs/Cost–effectiveness

In 2015, the MSF International Medical Products Price Guide (45) reported a median buyer price for zoledronic acid 4 mg/5 mL vial of US$ 23.45 in 2015.

Availability

Ibandronate and clodronate are not approved in USA.

Other considerations

Treatment should be continued throughout the course of the disease. However, to reduce the risk of treatment complications, interruption after 12–24 months should be considered in patients in remission and restarted on progression (*46, 47*).

Administration of zoledronic acid every 12 weeks may be as effective as the approved 4-weekly schedule (*48–50*).

Committee recommendations

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.

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8.3: Hormones and antihormones

Enzalutamide – rejection – EML

Enzalutamide **ATC Code: L02BB04**

Proposal

The application requested the addition of enzalutamide to the Complementary List of the EML as first-line therapy for the treatment of patients with metastatic castration-resistant prostate cancer who have not received chemotherapy or who have previously received docetaxel.

Applicant(s)

Knowledge Ecology International (KEI)

WHO technical department

WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

EML/EMLc

EML

Section

8.3 Hormones and antihormones

Dose form(s) and strength(s)

Capsule: 40 mg

Core/Complementary

Complementary

Individual/Square box listing

Individual

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

Enzalutamide was not included in the review of cancer medicines considered by the Expert Committee in 2015. Following that review, bicalutamide was added to the EML with a square box as representative of the pharmacological class of antiandrogens.

Despite enzalutamide being classified by the Anatomical Therapeutic Chemical (ATC) classification system as an antiandrogen and grouped with bicalutamide and similar agents, its mechanism of action differs from that of the other antiandrogens. Enzalutamide

should not be considered as an alternative to bicalutamide under the square box listing.

Bicalutamide is a non-steroidal, first-generation oral antiandrogen and is approved for use in conjunction with luteinizing hormone-releasing hormone (LHRH) analogues in men with hormone-treatment-naive prostate cancer. Bicalutamide has partial affinity for the androgen receptor and drug resistance can develop easily. Enzalutamide is a second-generation antiandrogen, with higher affinity for androgen receptors, resulting in modification of several steps in the androgen receptor signalling pathway and inhibition of cancer growth (*1*).

Public health relevance (burden of disease)

Prostate cancer is one of the most common cancers. In 2012, approximately 1.1 million men were diagnosed with prostate cancer; there are more than 300 000 estimated deaths annually (*2*). Prevalence varies hugely with geography and ethnicity, which may be attributed to differences in genetic susceptibility or to external factors, such as environment and differences in health care. The mean age of men with prostate cancer is 72–74 years (*3*).

Generally, the early stages of prostate cancer are slow growing and many go undiagnosed until a clinical autopsy is performed. Although most patients in resource-abundant regions are diagnosed with localized (and potentially curable) disease, patients in resource-limited regions typically present with advanced disease.

Androgen suppression, via either surgical or medical castration, is the mainstay for advanced disease. The effect of androgen suppression or castration on prostate cancer progression is finite and the disease will eventually progress from "castration-sensitive" to "castration-resistant". Despite initial response rates of 80–90%, nearly all men eventually develop progressive disease following androgen suppression.

Castration-resistant prostate cancer, potentially treated with the addition of chemotherapy, is characterized by a median overall survival of between 1 and 2 years.

Summary of evidence – benefits (from the application)

Enzalutamide is a second-generation competitive androgen receptor (AR) inhibitor. It antagonises the AR signalling thereby interfering with crucial elements that contribute to cancer progression (*4*). Enzalutamide has a half-life of 5.8 days; it is metabolized by cytochromes P450 2C8 and 3A4 and the drug steady state is reached in 28 days (*5*).

When prostate cancer is diagnosed and treated early and if tumours are localized, the prognosis is often favourable. However, some patients will relapse which, in nearly all cases, leads to castration-resistant prostate cancer (CRPC). At the CRPC stage, the disease is no longer responsive to androgen deprivation therapy (ADT), thus limiting the available treatment options and giving rise to a greater disease burden. Access to second-generation therapies such as enzalutamide provide a potential option for prolonging the life of the patient.

The application searched for systematic reviews, technology assessment reports and meta-analyses of controlled clinical trials involving enzalutamide in at least one arm. There were no meta-analyses reporting exclusively on enzalutamide-containing trials but a number

were found that compared enzalutamide, abiraterone (although not head-to-head) and other therapies in various treatment exposure settings. Key randomized controlled trials were summarized, together with a meta-analysis comparing enzalutamide with another second-generation inhibitor.

The AFFIRM clinical trial was a phase III randomized, double-blind, placebo-controlled, multicentre trial that studied the efficacy and safety of enzalutamide in patients with metastatic CRPC (mCRPC) who had previously taken docetaxel (*6*). Of 1199 adult males, aged 41–92 years, randomized in a 2:1 ratio, 800 received a dose of 160 mg of enzalutamide once a day, 399 received a placebo, and all participants continued on androgen deprivation therapy. Overall survival (OS) was 18.4 months for enzalutamide and 13.6 months for the control arm (hazard ratio (HR) 0.63; 95% confidence interval (CI) 0.53–0.75). Progression-free survival (PFS) was 8.3 months for enzalutamide versus 2.9 months for the placebo (HR 0.40; 95% 0.35–0.47). In the treatment arm, 54% of patients experienced 50% or greater reduction in prostate-specific antigen levels compared with only 2% in the control arm. The trial was stopped at the interim analysis, having demonstrated an improved OS. The results from the AFFIRM trial formed the basis for the initial approval by the U.S. Food & Drug Administration (FDA).

PREVAIL investigated enzalutamide in a first-line setting in mCRPC patients who had not yet received chemotherapy (*7*). This pivotal phase III, placebo-controlled clinical trial enrolled 1717 patients who were randomized 1:1. As with AFFIRM, PREVAIL was stopped early for benefit after interim results were collected. Fewer deaths were reported in the treatment arm (28% vs 35% for placebo; HR: 0.71; 95% CI 0.60–0.84]. Median OS was estimated at 32.4 months in the enzalutamide group and 30.2 months in the placebo group. At 12 months of follow-up, the rate of (radiographic) PFS was 65% in the enzalutamide group and 14% in the placebo group (risk of radiographic progression or death: HR 0.19; 95% CI 0.15–0.23). The benefit of enzalutamide was shown with respect to all secondary end-points. Based on the results of this trial, the FDA approved enzalutamide for used in first-line therapy for mCRPC.

Two studies compared enzalutamide with bicalutamide. A total of 396 men with non-metastatic or metastatic CRPC were randomly assigned to enzalutamide or bicalutamide (*8*). Enzalutamide reduced the risk of progression or death when compared with bicalutamide (HR 0.24; 95% CI 0.18–0.32). Median PFS was estimated at 19.4 months with enzalutamide and 5.7 months with bicalutamide. Enzalutamide resulted in significant improvements in all secondary outcomes. In a second study, 375 patients were randomly assigned to enzalutamide and bicalutamide (*9*). Patients in the enzalutamide group had significantly improved median PFS (HR 0.44; 95% CI 0·34–0·57) of 15.7 months compared with 5.8 months with bicalutamide.

Summary of evidence – harms (from the application)

Overall, enzalutamide seems to be well tolerated. In the AFFIRM trial adverse events of grade 3 or above were reported (45.3% of the enzalutamide group vs 53.1% of the placebo group) (*6*). Rates of adverse events were similar in the two groups despite the period of observation for the enzalutamide group being more than twice that for the placebo group. Grade ≥3 events relating to fatigue (6% vs 7%), diarrhoea (1% vs <1%), musculoskeletal pain (1% vs <1%), headache (<1% vs 0%) and seizures (0.6% vs 0%) occurred slightly more

often in the enzalutamide arm. Adverse events associated with patient death occurred in 3% in the enzalutamide arm and 4% in the placebo arm. Cardiac disorders were rare (1% vs 2%). The median time to the first such adverse event was 12.6 months in the enzalutamide group, compared with 4.2 months in the placebo group. The PREVAIL data for harm were similar: adverse events of grade 3 or above occurred in 43% of the enzalutamide vs 37% of the placebo group (*7*). The median time to the first event of grade 3 or higher was 22.3 months in the enzalutamide group and 13.3 months in the placebo group, again with longer exposure of patients to enzalutamide. The most common event of grade 3 or higher in the enzalutamide group was hypertension, which was reported in 7% of the patients. Other severe cardiac adverse events were infrequent and similar across groups (3% vs 2%). The most common adverse events leading to death were disease progression and a general deterioration in physical health, with similar incidences in the two groups.

Both the AFFIRM and the PREVAIL trials included quality of life as a secondary end-point. In the AFFIRM trial, a quality-of-life relevant improvement was seen more frequently with enzalutamide than placebo (43% vs 18%; $P < 0.001$). In the PREVAIL trial, patients on the enzalutamide arm had a delayed time to relevant decline in the quality of life (11.3 months vs 5.6 months; HR 0.63; $P < 0.001$).

Additional evidence (not in the application)

N/A

WHO guidelines

N/A

Costs/Cost–effectiveness

When sourced from Astellas under the brand name Xtandi, enzalutamide is expensive, with a wholesale price in USA of about US$ 10 549 for a supply of 120 capsules (*10*). Four 40-mg capsules of enzalutamide are administered orally daily.

Enzalutamide could be marginally cost effective compared with abiraterone or with best supportive care. Incremental cost-effectiveness ratios (ICERs) vary from country to country. In the United Kingdom, ICERs range from about US$ 19 000 per quality-adjusted life year (QALY) gained for enzalutamide when compared with abiraterone to US$ 55 000 per QALY gained for enzalutamide compared with supportive care (*11*). In North America, best estimate of ICER per QALY gained for enzalutamide when compared with supportive care exceeds US$ 100 000 (*12, 13*).

These studies are not particularly useful for decisions on the cost–effectiveness of enzalutamide in low-resource settings, particularly if the drug is available at a much lower price from generic suppliers. The application estimated that, with competition between generic suppliers and efficient procurement policies, prices for enzalutamide could fall to less than US$ 1 per day for a 4 x 40-mg dose.

Availability

Enzalutamide has several advantages over the other treatments for CRPC. For example, docetaxel requires IV administration; use of radium-223 and radiopharmaceuticals is often confined to tertiary-level care facilities. Enzalutamide and abiraterone acetate are the only daily oral tablets, and the pill burden is lighter with enzalutamide since it does not need to be taken in combination with prednisone.

Other considerations

N/A

Committee recommendations

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).

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Section 10: Medicines affecting the blood

10.1: Antianaemia medicines

Erythropoiesis-stimulating agents – addition – EML and EMLc

Erythropoietin-stimulating agents (ESAs)

Erythropoietin	**ATC Code: B03XA01**
Darbepoetin alfa	**ATC Code: B03XA02**
Methoxy polyethylene glycol-epoetin beta	**ATC Code: B03XA03**

Proposal

The application requested the addition of erythropoiesis-stimulating agents to the core list of the EML and EMLc for treating anaemia of chronic kidney disease in children, young people and adult patients with chronic renal disease requiring dialysis.

Applicant(s)

Rita Banzi, Chiara Gerardi, Vittorio Bertelé, Silvio Garattini, Arrigo Schieppati, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Italy; Rare Disease Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy

WHO technical department

Management of Noncommunicable Diseases, Violence and Injury Prevention

EML/EMLc

EML and EMLc

Section

10.1 Antianaemia medicines

Dose form(s) and strength(s)

EML:

- Erythropoiesis-stimulating agents*

Injection (pre-filled syringe): 1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL

* The square box applies to epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta and their respective biosimilars.

EMLc:

- Erythropoiesis-stimulating agents*

Injection (pre-filled syringe): 1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL

* The square box applies to epoetin alfa and beta, darbepoetin alfa and their respective biosimilars.

Erythropoiesis-stimulating agents (ESAs) are available as a solution for IV or SC injection.

Core/Complementary

Core

Individual/Square box listing

The application proposes a square box listing with therapeutic alternatives limited to:

- epoetin alfa and zeta
- epoetin beta
- epoetin theta (EML only)
- darbepoetin alfa
- methoxy polyethylene glycol-epoetin beta (CERA) (EML only)

The intention of square box listings is to limit options to alternatives within the same pharmacological class.

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

The antianaemia medicines currently included in the EML are: ferrous salt, ferrous salt + folic acid, folic acid, and hydroxocobalamin (*4*).

Public health relevance (burden of disease)

Chronic kidney disease is defined as the presence of kidney damage (usually detected as urinary albumin excretion ≥30 mg/day, or equivalent) or reduced kidney function (defined as estimated glomerular filtration rate (GFR) <60 mL/min per 1.73 m2) for 3 or more months, irrespective of the cause.

The prognosis for chronic kidney disease and the need for renal replacement therapy (either dialysis or kidney transplant) depend on: the cause of chronic kidney disease; GFR category; albuminuria category; and other risk factors and comorbid conditions (e.g. hypertension, hyperglycaemia, dyslipidaemia, smoking, obesity, history of cardiovascular disease) (*2*). End-stage renal disease refers to people with stage 5 chronic kidney disease undergoing dialysis and to recipients of kidney transplants. The KDIGO (Kidney Disease: Improving Global Outcomes) initiative recommends beginning dialysis as soon as life-threatening changes occur in fluid, electrolyte and acid–base balance; these usually happen when GFR is 5–10 mL/min per 1.73 m2. Specifically, starting dialysis is suggested when at least one of the following occurs:

- signs or symptoms of renal failure, such as serositis, acid–base or electrolyte abnormalities, pruritus
- inability to control volume status

- inability to control blood pressure
- malnutrition not responsive to dietary interventions
- cognitive impairment.

Anaemia is one of the most serious complications of chronic kidney disease and end-stage renal disease. Normochromic normocytic anaemia is due mainly to erythropoietin deficiency which itself is caused principally by reduced renal erythropoietin production, presumably reflecting the reduction in the number of erythropoietin-producing cells in the kidneys. To a lesser degree, it is caused by the shortened red cell lifespan. Erythropoietin is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow, and renal anaemia can thus be regarded as a hormone deficiency state.

According to WHO (*5*) anaemia is to be diagnosed when Hb falls below:

- 13 g/dL (130 g/L) in men ≥15 years old
- 12 g/dL (120 g/L) in non-pregnant women ≥15 years old or adolescents aged 12–14 years
- 11.5 g/dL (115 g/L) in children aged 5–11 years
- 11 g/dL (110 g/L) in pregnant women, or children aged 6-59 months.

If left untreated, anaemia in chronic kidney disease may cause deterioration in cardiac function, poor cognition and mental acuity, and fatigue. There are also associations with an increased risk of morbidity and mortality, principally due to cardiac disease and stroke (*6*).

Chronic kidney disease affects approximately 8–16% of the adult population worldwide (*7*). The overall lifetime incidence of chronic kidney disease rises with age, with approximately 50% of Stage 3a+ incidents occurring after age 70 years. The overall lifetime incidence of end-stage renal disease has been estimated at 3.6% (*8*). The incidence and prevalence of chronic kidney disease seem remarkably consistent globally, if not always well documented, whereas the distribution of those receiving renal replacement therapies (dialysis and transplantation) varies by country. About 2.2 million people receive dialysis globally, projected to be 5.4 million by 2030 (*9*).

Anaemia is one of the several complications of chronic kidney disease. Its prevalence (from any cause) in patients with renal failure is about 15% in USA (*10*). In chronic kidney diseases end stages, about half of all patients are severely anaemic.

The main impact of anaemia on organ function is reduced oxygen delivery to tissues, leading to debilitating symptoms such as fatigue, exercise intolerance, impaired cognitive function, sleep disorder, altered haemostasis, and depressed immune function. Anaemia in patients with chronic kidney disease is associated with decreases in cardiac and renal functions and impaired quality of life and poses a significant clinical and economic burden on health-care systems. Anaemia is also associated with a high prevalence of cardiovascular diseases in renal patients, with consequent higher morbidity and mortality: cardiovascular diseases are reported to account for more than 50% of deaths in these patients (*11*). In children, iron deficiency and Hb lower than 11.8 g/dL (118 g/L) have also been associated with cognitive impairment (*12*).

Summary of evidence – benefits (from the application)

The application summarizes evidence on the effectiveness and safety of ESAs, including

branded medicinal products and biosimilars, for the treatment of anaemia in end-stage chronic kidney disease in adults and children undergoing dialysis.

The review includes up-to-date systematic reviews of randomized controlled trials (RCTs) and other types of evidence syntheses (e.g. health technology assessment (HTA) reports, clinical guidelines if developed following a systematic approach) and pharmacoeconomic analyses comparing erythropoietins (epoetin alfa, beta, theta, zeta), darbepoetin alfa, and CERA with:

- no intervention, placebo, standard care
- other ESAs
- other interventions (e.g. iron supplementation, androgen)
- different dosages and administration schedules of the same ESA
- branded versus biosimilar products.

Eight systematic reviews (*13–20*), three clinical guidelines (*1, 6, 21*), two HTA reports (*22, 23*), five cost-analyses (described in the Costs section), one RCT published in 2015 but not included in the evidence synthesis reports (*24*) and one meta-regression study (*25*) were included.

Adults

Several sources of information provided useful information (*16, 18, 20, 24*), but the main source was a 2014 network meta-analysis that summarizes 56 studies for a total of 15 596 participants (*17*). This compared the efficacy and safety of different ESAs (epoetin alfa and beta, darbepoetin alfa, or CERA, and biosimilar ESAs, with each other, with placebo or with no treatment).

Epoetin alfa and beta vs placebo/no treatment/standard care (see Summary of Findings 1)

The evidence suggests that there are no differences in all-cause mortality and major cardiovascular events (stroke, myocardial infarction), presumably because of a paucity of data on these outcomes. Epoetin alfa and beta consistently reduced the risk of requiring blood transfusions. They do not appear to affect the risk of vascular access thrombosis but increase the risk of hypertension. The quality of evidence was judged to be low for all-cause mortality, major cardiovascular events and vascular access thrombosis because of the unclear risk of selection bias and the imprecision of the estimates. The effect of epoetin alfa and beta in reducing the number of blood transfusions and increasing the risk of hypertension was supported by high-quality evidence. However unclear, the risk of selection bias appears negligible in the light of the magnitude of these effects. These results seem to be consistent between industry-sponsored and other sponsorship trials.

Darbepoetin vs other ESAs (epoetin alfa and beta, CERA) (see Summary of Findings 2)

There is no evidence of a difference between darbepoetin and other ESAs (epoetin alfa, beta, CERA) in terms of all-cause mortality, major cardiovascular events (stroke, myocardial infarction), hypertension, vascular access thrombosis and Hb levels. The evidence suggests that darbepoetin reduces the risk of requiring blood transfusions compared with epoetin alfa but not with CERA. The quality of evidence was judged to be very low to moderate, mainly because of the unclear risk of selection bias, the imprecision of the estimates and the suspicion of selective reporting of outcomes. It is worthy of note that the effect of darbepoetin in reducing blood transfusions was supported by high-quality evidence.

These results were driven largely by industry-sponsored trials.

CERA vs epoetin alfa and beta (see Summary of Findings 3)

CERA appears to be similar to epoetin alfa and beta in terms of all the outcomes evaluated. However, the quality of evidence supporting these findings was judged to be very low and low because of the unclear risk of selection bias, the imprecision of the estimates and the suspicion of selective reporting of outcomes. These results were driven largely by industry-sponsored trials.

Originators (epoetin alfa) vs biosimilars (see Summary of Findings 4)

There were no differences between the originator epoetin alfa and its biosimilars in terms of all-cause mortality, major cardiovascular events (stroke, myocardial infarction), blood transfusions and vascular access thrombosis. The risk of hypertension seemed lower with biosimilars. The quality of evidence was generally judged to be low because of the unclear risk of selection bias and the imprecision of the estimates; the exception was the findings on hypertension, supported by evidence of moderate quality due only to unclear risk of selection bias. These results appear to be consistent between industry-sponsored and other sponsorship trials.

Quality of life

A systematic review updated to November 2015 specifically assessed the effect of achieving higher Hb targets on quality of life of patients with chronic kidney disease, including those undergoing dialysis (*14*). Of the 17 studies considered, 12 were in the non-dialysis population, four in the dialysis population, and one in a combined sample. Overall, the review showed that higher versus lower Hb targets resulted in only small and, in many cases, nonsignificant changes in scores of several health-related quality-of-life tools, both in the overall population and in the 2433 patients undergoing dialysis. In the latter subgroup, differences in physical functioning, vitality and social functioning measured as components of SF-36 (36-Item Short Form Health Survey) were 1.65 (95% confidence interval (CI) −7.22 to 10.52), −1.73 (95% CI −13.95 to 10.49), and −0.70 (95% CI −21.19 to 19.79), respectively. Differences were not statistically significant in the subgroup analysis that included only studies with low risk of bias.

Immunogenic potential (risk of developing anti-drug antibodies)

Biosimilars appear substantially equivalent to epoetin alfa in terms of Hb response and requirements for blood transfusion (see Summary of Findings 4). The quality of evidence supporting these findings is generally low. There are some concerns about the different potential risk for developing drug-associated antibodies, especially with regard to the interchangeability of originators and biosimilars and switching from one to the other. These concerns were addressed in a comprehensive systematic review of immunological reactions induced by treatment with biosimilar ESAs in patients with chronic kidney disease (*13*). The review included 14 RCTs and seven observational studies; 14 studies involved patients with end-stage renal disease undergoing dialysis. None of these studies indicated any important difference in efficacy between the original product and its biosimilar. Drug-associated antibodies were found in six of the 14 RCTs and six of the seven observational studies. However, the authors noted that inadequate and non-validated analytical methods were applied. No data were available on the clinical implications and reversibility of drug-

associated antibodies and induction of resistance, and no data demonstrated immunological or clinical consequences of switching between products.

Children

Although children differ substantially from adults, those caring for adult and paediatric patients with chronic kidney disease share largely the same concerns regarding the diagnosis and management of anaemia. Since evidence in children is generally scarce and of low quality, generalization from evidence in adults is unavoidable. A 2010 review identified two RCTs in children with end-stage renal disease (*26, 27*); a 2014 review by the same authors included one additional study on darbepoetin (*28*). Additional information can be found in the *Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease* issued by the National Kidney Foundation, which include non-randomized studies and data from registries (*21*).

The most robust evidence for using ESA products in children is related to epoetin alfa and beta, with some preliminary data on darbepoetin. Compared with epoetin in children with chronic kidney disease stages 4 and 5, darbepoetin alfa had uncertain effects on the need for blood transfusion and risk of progression to renal replacement therapy, all-cause mortality, hypertension, dialysis vascular access thrombosis, exceeding Hb target level and injection site pain, as well as Hb levels during treatment (*18*).

Children in the North American Pediatric Renal Transplant Cooperative Study database from 1992 to 2001 with Hb lower than 9.9 g/dL compared with those with Hb more than 9.9 g/dL had a high risk for mortality (adjusted relative risk, 1.52; 95% CI 1.03–2.26). Patients with more severe anaemia also had an increased risk of hospitalization.

In a multicentre single-arm interventional trial evaluating 22 children (4 months to 16 years) with chronic kidney disease, treatment of anaemia with recombinant erythropoietin was associated with a significant increase in intelligence quotient, although the relative increase in Hb levels was small (Hb baseline 9.2 ± 1.6 vs final 9.7 ± 1.7 g/dL) (*21, 29*).

Summary of evidence – harms (from the application)

The main safety concern linked to the use of ESAs in patients with chronic kidney disease is increases in the risk of death, myocardial infarction, stroke and other serious cardiovascular events. This is related to ESA doses targeting Hb of 11 g/dL and above. No trial has identified a Hb target level, ESA dose or dosing strategy that does not raise these risks. The lowest effective dose is therefore recommended (*30*).

All proprietary ESAs raised the odds of hypertension compared with placebo, while the effect of biosimilar ESAs on hypertension was less certain (*17*).

Since 2000, cases of aplasia (i.e. pure red cell aplasia, PRCA) and severe anaemia, with or without cytopenia, associated with neutralizing antibodies to erythropoietin, were reported in Europe and in USA, primarily in patients with chronic kidney disease given the medicine by SC injection. This was probably due to the interaction of stabilizing agent and part of the pre-filled syringes. Despite modifications in the pre-filled syringes new cases of antibody-associated PRCA are still reported, although the size of the phenomenon is limited (*31*). Based on time of exposure, PRCA incidence was 35.8/100 000 patient-years (95% CI 7.4–

104.7) for epoetin alfa, 14.0/100 000 patient-years (95% CI 1.7–50.6) for epoetin beta and darbepoetin (*11*). No cases of PRCA emerged from the clinical development of biosimilars of epoetin alfa. However, sudden loss of efficacy and confirmed cases of PRCA were reported in a cluster of 23 Thai patients receiving regionally manufactured SC epoetin not approved in Europe (*32, 33*).

High doses of erythropoietin may be associated with nephrogenic fibrosing dermopathy (*34*).

A major issue in ESA use relates to the Hb target. It is generally known that targeting higher Hb levels in chronic kidney disease raises the risks for stroke, hypertension and vascular access thrombosis and probably increases the risks of death, serious cardiovascular events and end-stage renal disease (*19*). A systematic review with meta-regression of RCTs of ESAs in patients with chronic kidney disease examined whether a gradient of doses was associated with these potential harms, adjusting for the target or achieved Hb level (*25*). The authors identified an association between the first 3-month and total study period mean ESA dose and all-cause mortality, both in unadjusted models and models adjusting for target Hb. When restricting the analyses to dialysis patients, the association persisted in both the unadjusted and adjusted analyses. The lack of adjustment for other factors such as comorbidities and inflammatory markers, and inadequate control for treatment-by-indication bias and ecological fallacy, are limitations of this meta-regression analysis. In any case, these findings support the widely accepted use of more conservative dosing regimens for the treatment of patients with chronic kidney disease. Recent systematic reviews have suggested that aiming at Hb levels similar to those in healthy adults involves a significantly higher risk of all-cause mortality (*16, 19*).

The first-generation ESAs (epoetin alfa and epoetin beta) have to be administered frequently, up to three times a week. This led to development of ESA agents with longer half-life (darbepoetin alfa, CERA) and consequent lower dosing frequency. The dosing schedules of darbepoetin once a week or once every 2 weeks and of CERA once a month offer many potential advantages to both patients and caregivers (*35*). However, the impact of these advantage should be considered in the light of the frequency of dialysis, which for most patients is three times a week.

It remains unclear whether the new, longer-acting ESAs, given less frequently, offer the same efficacy and safety as older ESAs. A Cochrane systematic review updated in 2013 (*16*) sought to establish the optimal frequency of ESA administration. The review included 33 studies involving 5526 participants and concluded that longer-acting ESA (darbepoetin and CERA) given at 1–4-week intervals were non-inferior to ESA given 1–3 times a week in terms of achieving Hb targets, without any significant differences in adverse events in haemodialysis patients.

The rapidly growing clinical experience with biosimilars has confirmed that their safety profile is in line with that of the reference products in terms of cardiovascular and thromboembolic events and immunogenicity data. In general, the known safety profile of ESAs as a class can be extended to biosimilars (*36*).

Additional evidence (not in the application)

N/A

WHO guidelines

N/A

Costs/Cost–effectiveness

The application identified five cost-analyses. Four of them (37–40) and two HTA reports (*22, 23*) form the basis of the evidence reported here.

Studies that evaluated different Hb targets showed that achieving higher Hb is not a cost-effective strategy, with mortality, hospitalization and utility estimates as major drivers of costs. When the initial Hb levels in haemodialysis patients were below 9 g/dL, providing epoetins in order to reach 10 to 11 g/dL was less costly and more effective than higher or lower Hb levels. Reported cost/QALY (quality-adjusted life- year) ratios ranged from US$ 931/QALY to US$ 677 749/QALY across five studies comparing ESAs with red blood cell transfusions.

One retrospective study on the relative utilization and cost of ESAs in patients switched from epoetin to darbepoetin showed that the median dose:conversion ratio for each haemodialysis centre ranged from 288:1 to 400:1 and the average annual per-patient saving from US$ 2140 to US$ 4711. The authors concluded that switching patients from epoetin to darbepoetin maintained clinical benefits while considerably reducing costs. The study was conducted by independent researchers with an unrestricted grant from the darbepoetin producer (*39*).

Another systematic review examined whether once-monthly CERA gave better cost–effectiveness or even cost saving compared with other ESAs. Review findings were contradictory, some demonstrating an increase in costs associated with CERA and others a cost reduction (*40*).

It is expected that the introduction of biosimilars of epoetin will have an impact on prices and drug market. Price differences between biosimilars and originators has been broadly estimated at between 10% and 34%, although current evidence is limited (*41*).

An estimate of biosimilar-related savings from 2007 to 2020 in eight European countries (Germany, France, Italy, Poland, Romania, Spain, Sweden and United Kingdom) was provided in a report supported by Sandoz Pharmaceuticals (*42*). On the basis of the data provided by IMS Health, the report evaluated how biosimilars can help in reducing health-care expenditure over the long term, through the increased use of biosimilars rather than originators. The estimated cumulative saving for biosimilar epoetins was €9.4–11.2 billion, subject to the expected market share trend and scenarios. The expected savings amount to 21.4–25.5% of the estimated €43.8 billion expenditure without the market entry of biosimilars.

Cost saving should be weighted and evaluated considering the different penetration of biosimilars in different countries. IMS data up to 2011 showed that overall biosimilar sales are still a relatively small segment of the European market but that annual growth is strong. For epoetins, the highest uptake was reported in Germany, Greece and Sweden (*43*).

Availability

ESAs are licensed globally for treatment of symptomatic anaemia associated with chronic kidney disease.

With the expiry of patent protection for epoetin alfa in Europe in 2007, biosimilar erythropoietins – e.g. epoetin alfa (Binocrit, Abseamed, Epoetin alfa Hexal), epoetin zeta (Retacrit, Silapo) – were introduced on the market (*36*). The patents on darbepoetin (Aranesp) expired in Europe in 2016 and will expire in USA in 2024 (*42*). Darbepoetin alfa "similar biologic" drugs (Actorise, Cresp, Darbatitor) are available in India (*42*).

To be licensed in countries with stringent regulatory agencies, such as USA and countries of the European Union, a new epoetin claimed to be similar to a reference marketed product needs to undergo a proper comparability exercise, i.e. the head-to-head comparison, to establish similarity in quality, safety and efficacy (*44*). The stringent regulatory criteria and the need to provide a comprehensive data package have often been seen as putting an unnecessary burden (and cost) on the development and licensing processes, leading to delays in access to biosimilars. On the other hand, these criteria are meant to provide a sufficient level of evidence and extrapolation to reduce the concerns of both patients and health-care professionals about the use of biosimilars. Nevertheless, the adoption of such criteria is a matter of debate in clinical practice, with particular regard to the acceptability of switching from a reference drug to its biosimilars. However, pre-marketing trials and, above all, post-marketing drug-utilization data have helped, consolidating not only the therapeutic equivalence of the two products but also the safety of switching from reference to biosimilar products (*45–47*).

Other considerations

The application did not include peginesatide because of the safety concerns reported post-marketing, including serious hypersensitivity reactions such as anaphylaxis, which may be life-threatening or fatal. In 2013, the FDA recalled all lots of injectable peginesatide (Omontys) because of 19 reports of anaphylaxis (including three deaths) after the first dose in patients receiving dialysis (*48*).

Committee recommendations

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).

Summary of findings 1: Epoetin alfa or beta compared with placebo/no treatment/standard care for anaemia of end-stage kidney disease in dialysis patients						
Patient or population: dialysis patients with anaemia of end-stage kidney disease						
Intervention: epoetin alfa or beta			*Comparison*: placebo/no treatment/standard care			
Outcomes	***Anticipated absolute effects[a] (95% CI)***		***Relative effect[b] (95% CI)***	***No. of participants (studies)***	***Quality of the evidence (GRADE)***	***Comments***
	Risk with placebo/no treatment/standard care	***Risk with epoetin alfa or beta***				
All-cause mortality	61 per 1000	48 per 1000 (26–87)	OR 0.78 (0.41–1.48)	774 (4 RCTs)	⊕⊕◯◯ LOW [c,d]	
Major cardiovascular events	19 per 1000	6 per 1000 (0–136)	OR 0.33 (0.01–8.21)	106 (1 RCT)	⊕⊕◯◯ LOW [c,d]	
Blood transfusions	437 per 1000	30 per 1000 (8–104)	OR 0.04 (0.0–0.15)	329 (3 RCTs)	⊕⊕⊕⊕ HIGH [c,e]	
Vascular access thrombosis	58 per 1000	121 per 1000 (24–443)	OR 2.23 (0.39–12.88)	217 (2 RCTs)	⊕⊕◯◯ LOW [c,d]	
Hypertension	83 per 1000	245 per 1000 (171–338)	OR 3.59 (2.29–5.64)	843 (5 RCTs)	⊕⊕⊕⊕ HIGH [c,e]	
Final/change in Hb level	Mean final/change in Hb level was 0	Mean final/change in Hb level in the intervention group was 0 (0–0	–	(0 studies)	–	

[a] Risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] CI: confidence interval; OR: odds ratio
[c] Unclear risk of selection bias.
[d] Small number of events, 95% CI includes 1.
[e] Large magnitude of effect.

Summary of findings 2: Darbepoetin compared with other ESAs for anaemia of end-stage kidney disease in dialysis patients						
Patient or population: dialysis patients with anaemia of end-stage kidney disease						
	Intervention: darbepoetin		*Comparison*: other ESAs			
Outcomes	***Anticipated absolute effects[a] (95% CI)***		***Relative effect[b] (95% CI)***	***No. of participants (studies)***	***Quality of the evidence (GRADE)***	***Comments***
	Risk with other ESAs	***Risk with darbepoetin***				
All-cause mortality – darbepoetin vs epoetin alfa or beta	54 per 1000	69 per 1000 (50 to 93)	OR 1.29 (0.93–1.80)	2639 (12 RCTs)	⊕◯◯◯ VERY LOW [c,d,e]	
All-cause mortality – darbepoetin vs CERA	68 per 1000	65 per 1000 (38 to 108)	OR 0.95 (0.55–1.67)	798 (2 RCTs)	⊕⊕⊕◯ MODERATE [d]	
Major cardiovascular events – darbepoetin vs epoetin alfa	37 per 1000	20 per 1000 (9 to 46)	OR 0.53 (0.23–1.24)	1023 (2 RCTs)	⊕◯◯◯ VERY LOW [c,d,f]	
Major cardiovascular events – darbepoetin vs CERA	not pooled	not pooled	not pooled	(0 studies)	–	
Blood transfusions – darbepoetin vs epoetin alfa	83 per 1000	32 per 1000 (20 to 55)	OR 0.37 (0.22–0.64)	1269 (3 RCTs)	⊕⊕⊕⊕ HIGH [c,g]	
Blood transfusions – darbepoetin vs CERA	135 per 1000	128 per 1000 (88 to 180)	OR 0.94 (0.62–1.41)	802 (2 RCTs)	⊕⊕⊕◯ MODERATE [d]	
Vascular access thrombosis – darbepoetin vs epoetin alfa or beta	112 per 1000	109 per 1000 (78 to 150)	OR 0.97 (0.67–1.40)	1432 (3 RCTs)	⊕◯◯◯ VERY LOW [c,d,f]	

Vascular access thrombosis – darbepoetin vs CERA	90 per 1000	70 per 1000 (37–127)	OR 0.76 (0.39–1.47)	489 (1 RCT)	⊕⊕⊕◯ MODERATE [d]
Hypertension – darbepoetin vs epoetin alfa or beta	199 per 1000	205 per 1000 (166–249)	OR 1.04 (0.80–1.34)	1591 (4 RCTs)	⊕◯◯◯ VERY LOW [c,d,f]
Hypertension – darbepoetin vs CERA	123 per 1000	95 per 1000 (63–141)	OR 0.75 (0.48–1.17)	798 (2 RCTs)	⊕⊕⊕◯ MODERATE [d]
Final/change in Hb level – darbepoetin vs epoetin alfa	Mean final/change in Hb level was 0	Mean final/change in Hb level – darbepoetin vs epoetin alfa in the intervention group was 0.02 higher (0.09 lower to 0.12 higher)	–	1245 (6 RCTs)	⊕⊕◯◯ LOW [c,h]
Final/change in Hb level – darbepoetin vs CERA	Mean final/change in Hb level was 0	Mean final/change in Hb level – darbepoetin vs CERA in the intervention group was 0.3 lower (0.55 lower to 0.05 lower)	–	249 (1 RCT)	⊕⊕⊕◯ MODERATE [i]

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] CI: confidence interval; OR: odds ratio
[c] Unclear risk of selection bias.
[d] Small number of events, 95% CI includes 1.
[e] High risk of selective reporting bias (8 out of 12 studies).
[f] All studies at high risk of selective reporting bias.
[g] Large magnitude of effect.
[h] 95% CI includes zero.
[i] Sample size less than 400.

Summary of findings 3: CERA compared with other ESAs for anaemia of end-stage kidney disease in dialysis patients						
Patient or population: dialysis patients with anaemia of end-stage kidney disease						
	Intervention: methoxy polyethylene glycol-epoetin beta (CERA)		*Comparison*: other ESAs			
Outcomes	***Anticipated absolute effects[a] (95% CI)***		***Relative effect[b] (95% CI)***	***No. of participants (studies)***	***Quality of the evidence (GRADE)***	***Comments***
	Risk with other ESAs	***Risk with CERA***				
All-cause mortality – CERA every 2 weeks vs epoetins	62 per 1000	64 per 1000 (41–97)	OR 1.03 (0.65–1.62)	1341 (4 RCTs)	⨁◯◯◯ VERY LOW [c,d,e]	
All-cause mortality – CERA every 4 weeks vs epoetins	59 per 1000	68 per 1000 (42–107)	OR 1.16 (0.70–1.92)	1108 (3 RCTs)	⨁◯◯◯ VERY LOW [c,d,f]	
Blood transfusions – CERA every 2 weeks vs epoetins	90 per 1000	83 per 1000 (58–118)	OR 0.91 (0.62–1.35)	1341 (4 RCTs)	⨁◯◯◯ VERY LOW [c,d,e]	
Blood transfusions – CERA every 4 weeks vs epoetins	87 per 1000	87 per 1000 (55–134)	OR 1.01 (0.62–1.64)	827 (2 RCTs)	⨁⨁◯◯ LOW [d,g]	
Vascular access thrombosis – CERA vs epoetin beta	87 per 1000	51 per 1000 (15–164)	OR 0.57 (0.16–2.06)	181 (1 RCT)	⨁⨁◯◯ LOW [c,d]	
Hypertension – CERA vs epoetin beta	239 per 1000	185 per 1000 (91–337)	OR 0.72 (0.32–1.62)	181 (1 RCT)	⨁⨁◯◯ LOW [c,h]	
Final/change in Hb level – CERA every 2 weeks vs epoetins	Mean final/change in Hb level – CERA every 2 weeks vs EPO was 0	Mean final/change in Hb level – CERA every 2 weeks vs EPO in the intervention group was 0,08 higher (0,04 lower to 0,21 higher)	–	1126 (4 RCTs)	⨁◯◯◯ VERY LOW [c,e,i]	

Final/change in Hb level - CERA every 4 weeks vs EPO	Mean final/change in Hb level – CERA every 4 weeks vs EPO was 0	Mean final/change in Hb level – CERA every 4 weeks vs EPO in the intervention group was 0.03 lower (0.17 lower to 0.12 higher)	–	672 (2 RCTs)	⨁◯◯◯ VERY LOW [c,g,i]

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] CI: confidence interval; OR: odds ratio
[c] Unclear risk of selection bias.
[d] Small number of events, 95% CI includes 1.
[e] Three out of four studies reported ITT data only graphically.
[f] Two out of three studies reported ITT data only graphically.
[g] All studies reported ITT data only graphically.
[h] Sample size less than 400, 95% CI includes 1.
[i] 95% CI includes zero.

Summary of findings 4: Biosimilars compared with epoetin alfa for anaemia of end-stage kidney disease in dialysis patients						
Patient or population: dialysis patients with anaemia of end-stage kidney disease						
Intervention: biosimilars			*Comparison*: epoetin alfa			
Outcomes	***Anticipated absolute effects[a] (95% CI)***		***Relative effect[b] (95% CI)***	***No. of participants (studies)***	***Quality of the evidence (GRADE)***	***Comments***
	Risk with placebo/no treatment/standard care	***Risk with epoetin alfa or beta***				
All-cause mortality	37 per 1000	48 per 1000 (31–74)	OR 1.32 (0.83–2.09)	1883 (6 RCTs)	⊕⊕◯◯ LOW [c,d]	
Major cardiovascular events	69 per 1000	80 per 1000 (48–132)	OR 1.17 (0.67–2.04)	718 (3 RCTs)	⊕⊕◯◯ LOW [c,d]	
Blood transfusions	29 per 1000	40 per 1000 (24–66)	OR 1.41 (0.83–2.38)	1823 (3 RCTs)	⊕⊕◯◯ LOW [c,d]	
Hypertension	69 per 1000	39 per 1000 (23–66)	OR 0.55 (0.32–0.95)	1464 (4 RCTs)	⊕⊕⊕◯ MODERATE [c]	
Vascular access thrombosis	35 per 1000	24 per 1000 (10–58)	OR 0.69 (0.28–1.70)	823 (2 RCTs)	⊕⊕◯◯ LOW [c,d]	
Final/change in Hb level	Mean final/change in Hb level was 0	Mean final/change in Hb level in the intervention group was 0	–	(0 studies)	–	Outcome not reported in the analysed reviews

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] CI: confidence interval; OR: odds ratio

[c] Unclear risk of selection bias.

[d] Small number of events, 95% CI includes 1.

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Section 12: Cardiovascular medicines

12.3: Antihypertensive medicines

Lisinopril + hydrochlorothiazide – rejection – EML

Lisinopril + hydrochlorothiazide **ATC Code: C09BA03**

Proposal

The application proposed the addition of a fixed-dose combination formulation of lisinopril + hydrochlorothiazide to the core list of the EML for treatment of hypertension in patients not adequately controlled with monotherapy. It is recommended that patients be first stabilized on the component medicines at the same dosage before initiating treatment with the corresponding fixed-dose combination.

Listing was requested with a square box to represent the pharmacological classes of angiotensin-converting enzyme inhibitors and thiazide diuretics.

Applicant(s)

Abdul Salam and colleagues, The George Institute for Global Health, University of Sydney, Sydney, Australia

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WHO technical department

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

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EML/EMLc

EML

Section

12.3 Antihypertensive medicines

Dose form(s) and strength(s)

Tablet: 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg

Core/Complementary

Core

Individual/Square box listing

Square box listing

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

The pharmacological class of angiotensin-converting enzyme (ACE) inhibitors is represented on the EML with a square box listing for enalapril, which would capture lisinopril. Hydrochlorothiazide (HCTZ) is included on the EML with a square box listing as representative of thiazide diuretics.

Public health relevance (burden of disease)

Hypertension is the leading cause of preventable morbidity and mortality globally, and was the leading risk factor for global disease burden in 2010 (*1*). In 2015, there were more than 1 billion adults with raised blood pressure globally, compared with almost 600 million in 1975. Most of this increase is attributable to net increases in low- and middle-income countries (*2*). The benefits of lowering blood pressure in terms of reduced risk of cardiovascular events are well known, and there is evidence that a greater reduction in blood pressure is associated with a larger reduction in cardiovascular events (*3–6*).

Summary of evidence – benefits (from the application)

A literature search conducted by the applicants identified seven randomized controlled trials (RCTs) of lisinopril + HCTZ versus various comparator treatments in patients with hypertension.

Trials that compared the combination with placebo and/or with the component monotherapies all showed the combination to be associated with significant reductions in systolic and/or diastolic blood pressure (*7–10*). Four trials reported data for the comparison of lisinopril + HCTZ with other dual-combination therapies and showed the various dual combinations to be associated with similar blood pressure lowering efficacy (*8, 11–13*).

The effects of combination antihypertensive therapy (not necessarily lisinopril + HCTZ) compared with placebo or no treatment on cardiovascular outcomes (coronary heart disease (CHD), stroke, heart failure and mortality) were assessed in the application in a systematic review of 11 RCTs involving 35 208 patients (*14-24*). For all studies combined, the review found that combination antihypertensive therapy significantly reduced the risk of cardiovascular outcomes. The risks were reduced even further when only those trials that demonstrated a systolic blood pressure reduction of more than 6 mmHg (0.8 kPa) were considered.

Effects of combination therapy vs placebo on CHD, stroke, heart failure and death

	Studies	*Intervention: events/ participants*	*Control: events/ participants*	*RR (95% CI)*
Studies with >6 mmHg reduction in systolic blood pressure				
CHD	11	175/5585	240/5694	0.75 (0.62–0.91)
Stroke	11	310/5669	518/5694	0.61 (0.53–0.69)
Heart failure	08	66/3172	157/3879	0.48 (0.36–0.63)
Death	11	499/5596	627/5694	0.81 (0.72–0.90)
Studies with ≤6 mmHg reduction in systolic blood pressure				
CHD	2	317/11 925	356/11 920	0.90 (0.77–1.03)
Stroke	2	290/11 925	312/11 920	0.93 (0.80–1.10)
Heart failure	1	21/6356	29 / 6349	0.72 (0.41–1.27)
Death	2	750/11 925	820/11 920	0.91 (0.83–1.00)
All studies				
CHD	13	492/17 510	596/17 614	0.84 (0.74–0.94)
Stroke	13	600/17 594	830/17 614	0.73 (0.66–0.80)
Heart failure	9	87/9528	186/10 228	0.52 (0.40–0.67)
Death	13	1249/17 521	1447/17 614	0.87 (0.80–0.93)

RR = risk ratio; CI = confidence interval

Summary of evidence – harms (from the application)

The adverse effect profiles of ACE inhibitors and thiazide diuretics are well known. Safety data from the studies involving lisinopril + HCTZ presented in the application are consistent with the known adverse event profiles of ACE inhibitors and thiazides.

Additional evidence (not in the application)

N/A

WHO guidelines

A low-dose thiazide-like diuretic, ACE inhibitor or calcium-channel blocker is the recommended first-line antihypertensive therapy in the 2007 WHO *Pocket guidelines for assessment and management of cardiovascular risk* (*25*).

International treatment guidelines recommend consideration of antihypertensive therapy involving a combination of two or more drugs in patients with persistent or markedly high blood pressure or at high cardiovascular risk (*26, 27*).

Costs/Cost–effectiveness

2015 and 2016 sales data presented in the application indicate that lisinopril + HCTZ (strength unspecified) is the most commonly prescribed ACE inhibitor + diuretic combination, with the lowest average price per tablet (€0.07–0.08; the US$ equivalent is close to the same number).

According to the MSH International Medical Products Price Guide (*28*), the median buyer prices per tablet for lisinopril 10 mg and HCTZ 25 mg in 2014 were US$ 0.0353 and US$0.0094 (= US$ 0.0447 combined).

Availability

Wide global availability

Other considerations

The Expert Committee noted differences between the use of FDC therapies for treatment of communicable diseases compared with noncommunicable diseases (NCDs). The Committee also noted that pharmacological management of NCDs is complex: it is designed to treat the multiple conditions that a patient might have, must be tailored to the patient's clinical condition, and may require regular adjustments in dosage and schedule of individual components to maximize efficacy and minimize adverse effects. FDCs for communicable diseases (e.g. HIV/AIDS, tuberculosis, malaria, hepatitis C) are designed to target a specific, identified infectious agent and to minimize the development of resistance. Combination therapy is often essential in these conditions and, since components should not be given individually, less flexibility in doses and components is required in tailoring therapy for individual patients.

The Expert Committee considered that FDCs for NCDs may have advantages over the single medicines given concomitantly, including increased adherence and reduced pill burden. For this reason, the Committee recognized the potential value of FDCs that have regulatory approval and demonstrated bioavailability for the management of chronic NCDs. However, the Committee observed that many different combinations of cardiovascular medicines exist, with multiple permutations of components from different therapeutic classes, varying strengths and dosages. The Committee agreed that there is a need to develop the evidence base for FDCs in low- and middle-income countries, including procurement, utilization, cost–effectiveness and adherence (*29*).

Given this complexity, the Committee was firmly of the view that it would not be appropriate to list individual FDCs for NCDs on the EML as this would not provide the required flexibility for choosing optimal combinations and doses of multidrug therapy for cardiovascular disease. However, the Committee also recognized that, particularly for patients on established multidrug regimens, moving to an FDC containing the same products would probably improve adherence and that there should therefore be discretion at national level to make this choice.

Committee recommendations

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.

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Losartan – addition – EML

Losartan — ATC Code: C09CA01

Proposal

The application requested 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 tolerate angiotensin-converting-enzyme inhibitors.

Applicant(s)

Drs David Heller, Evan Blank, Matthew Cagliostro and Sandeep Kishore, Icahn School of Medicine at Mount Sinai, New York, USA; Dr Amisha Patel, Columbia College of Physicians and Surgeons, New York, USA.

The application was supported by Dr Peter Lamptey, London School of Hygiene and Tropical Medicine, Accra, Ghana, Drs Jagat Narula and Rajesh Vedanthan, Icahn School of Medicine at Mount Sinai, New York, USA, and Dr Salim Yusuf, Faculty of Health Sciences, McMaster University, Hamilton, Canada.

WHO technical department

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

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EML/EMLc

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Section

12.3 Antihypertensive medicines; 12.4 Medicines used in heart failure

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Dose form(s) and strength(s)

Tablet: 25 mg; 50 mg; 100 mg

Core/Complementary

Core

Individual/Square box listing

Square box

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

Angiotensin-receptor blockers (ARBs) had not previously been considered for inclusion on the EML.

Angiotensin-converting-enzyme (ACE) inhibitors have been included on the EML since 1990, when the pharmacological class was represented by captopril. In 2003, enalapril replaced captopril as the representative ACE inhibitor. ACE inhibitors are represented by enalapril in the current EML as antihypertensive medicines and medicines used in heart failure.

Enalapril (with a square box) has been included on the EMLc for the treatment of hypertension in children since 2009.

Public health relevance (burden of disease)

Hypertension is the leading risk factor for death worldwide (*1*), and the burden of hypertension disproportionately afflicts the world's poorest countries (*2–4*). Hypertension contributes to coronary heart disease, myocardial infarction, stroke, chronic kidney disease and heart failure, among other conditions. There is high-quality evidence that hypertension control is both effective and cost effective in reducing the risk of these conditions.

ACE inhibitors and ARBs are widely recommended in international evidence-based guidelines for the treatment of hypertension, heart failure and chronic kidney disease (CKD), especially in persons with diabetes.

The 2014 *Evidence-based guidelines for the management of high blood-pressure in adults*, authored by the Eighth Joint (US) National Committee recommend the use of ARBs or ACE inhibitors as possible first-line agents for essential hypertension, alone or in combination, for all non-black populations, and as definite first-line agents for essential hypertension for persons with CKD, regardless of race (*5*).

The 2013 European Society of Cardiology Guidelines on diabetes, pre-diabetes and cardiovascular diseases recommend ACE inhibitors or ARBs for persons with diabetes and hypertension, especially when there is concomitant coronary artery disease, to reduce morbidity and mortality (*6*).

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of heart failure and the 2016 European Society of Cardiology (ESC) guidelines for the treatment of acute and chronic heart failure recommend the use of ARBs for reduction of morbidity and mortality in patients with heart failure and reduced ejection fraction who are ACE inhibitor-intolerant (*7, 8*).

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for evaluation and management of CKD recommend either an ARBs or ACE inhibitors for all persons with CKD with urine albumin excretion of more than 300 mg/day, to prevent and control proteinuria and consequent nephropathy (*9*).

Summary of evidence – benefits (from the application)

The application stated that extensive high-quality data have demonstrated the efficacy of ACE inhibitors for the treatment of hypertension as well as primary and secondary prevention of cardiovascular disease (CVD) in individuals with diabetes mellitus, heart failure with reduced ejection fraction, and myocardial infarction (*10–12*). ARBs act on a near-identical biological pathway to ACE inhibitors, inhibiting the renin-angiotensin

system by blocking renal receptors for angiotensin instead of preventing its generation in the lung.

Hypertension

In a systematic review of 61 studies involving more than 15 000 patients no significant difference in blood-pressure lowering was found between ACE inhibitors and ARBs (*13*).

A 2014 Cochrane systematic review examined nine studies with 11 007 participants and found no significant difference between ACE inhibitors and ARBs with respect to total mortality, total cardiovascular events, or cardiovascular mortality among patients with hypertension (*14*). A 2016 systematic review of randomized trials of more than 250 000 patients without heart failure confirmed this result, finding no significant difference with respect to all-cause mortality, cardiovascular mortality and myocardial infarction (*15*). In addition, relative to placebo, ARBs were significantly associated with reduced risk of multiple hypertension sequelae such as heart failure, stroke and end-stage renal disease (*15*).

Heart failure

ACE inhibitors and ARBs are efficacious in secondary prevention of morbidity and mortality in patients with existing heart failure with reduced ejection fraction. A meta-analysis of five trials involving 12 763 patients with heart failure with reduced ejection fraction found that use of an ACE inhibitor substantially decreased risk of all-cause death, readmission for heart failure, and myocardial infarction (*16*). Similarly, a randomized trial of the ARB valsartan in chronic heart failure found a significant reduction, relative to placebo, in mortality and morbidity signs and symptoms of heart failure, and hospitalizations for treatment (*17*). Another trial by the VALIANT investigators showed non-inferiority of valsartan compared with captopril among patients with post-myocardial infarction with reduced ejection fraction (*18*).

The application stated that, on the basis of these and other data, the 2013 ACC/AHA guideline for the management of heart failure and the 2016 ESC guidelines for the treatment of acute and chronic heart failure recommend the use of ARBs for those with heart failure and reduced ejection fraction who are ACE inhibitor-intolerant (*7, 8*).

Chronic kidney disease (CKD)

In patients with CKD, ACE inhibitors and ARBs may be superior to other antihypertensives in the secondary prevention of cardiovascular events because, in addition to their impact on blood pressure control, they influence other renal sequelae, such as proteinuria. A meta-analysis of the effect of monotherapy and combination therapy with ACE inhibitors and ARBs for CKD in 6181 participants (*18*) found that they significantly, and with equal effectiveness, reduced proteinuria compared with both placebo and calcium channel blockers (ratio of means 0.66; 95% confidence interval (CI) 0.63–0.69; and ratio of means 0.62, 95% CI 0.55–0.7, respectively) over 5–12 months. The ESC/European Association for the Study of Diabetes guidelines on diabetes, pre-diabetes, and cardiovascular disease therefore recommend ACE inhibitors and ARBs for secondary prevention of CVD in patients with these conditions (*6*).

Summary of evidence – harms (from the application)

ACE inhibitor-mediated inhibition of pulmonary kininase activity frequently results in cough secondary to increased bradykinin (*19–21*). In addition, ACE inhibitors can cause angioedema in 0.1–0.8% of individuals, with up to five times greater frequency in people of African descent (*10, 11, 22, 23*).

Rates of adverse events with ARBs have been assessed relative to placebo and to ACE inhibitors.

In the ONTARGET trial comparing telmisartan with ramipril, telmisartan was associated with a greater mean decrease in blood pressure but a significantly higher rate of hypotensive symptoms. However, there was a lower rate of cough (1.1% vs 4.2%) and angioedema (0.1% vs 0.3%) with telmisartan than with ramipril (*10*). The rate of hyperkalaemia was 3% in both groups.

The TRANSCEND investigators examined 5926 patients deemed intolerant to ACE inhibitors and showed very low rates of both cough (0.5%) and angioedema (0.07%) associated with the ARB telmisartan, with no statistically significant difference in incidence of these side-effects when compared with the placebo group (*12*).

Both ACE inhibitors and ARBs are contraindicated in pregnancy; in the case of ARBs this is partly because of feedback disinhibition of renin release, which could activate the fetal AT2 receptor (*24*). There is evidence that olmesartan may rarely produce a sprue-like enteropathy, which resolves on cessation of the drug. A French cohort trial of some 4.5 million patients on olmesartan established a number-needed-to-harm (NNH) of 12 550 for olmesartan treatment to cause one case of severe enteropathy (*25*); there was no increased risk in users of other ARBs.

A 2014 Cochrane systematic review found high-quality evidence supporting a lower incidence of withdrawals due to all adverse effects (WDAE) for ARBs relative to ACE inhibitors (relative risk 0.83; 95% CI 0.74–0.93), accounted for mostly by a difference in the incidence of cough (*14*). A 2016 meta-analysis involving more than 250 000 patients from randomized trials found the relative risk of WDAE in ARBs relative to ACE inhibitors was 0.72 (95% CI 0.85–0.81), suggesting better tolerability of ARBs (*15*).

Additional evidence (not in the application)

N/A

WHO guidelines

N/A

Costs/Cost–effectiveness

Generic formulations of ARBs are now available, and the differences in costs between ARBs and ACE inhibitors is diminishing. The application notes that losartan has therefore followed the typical pattern of evolution of pricing for antihypertensives, with an 80–90% price reduction in the year after generics become available and gradual decreases in prices thereafter.

By way of comparison, the median buyer price for losartan 50 mg according to the MSH International Medical Products Price Guide (2015) was US$ 0.0181 per tablet/capsule, while that for enalapril 20 mg was US$ 0.0114 per tablet/capsule (*26*).

Availability

ARBs have been approved by stringent regulatory authorities including the U.S. Food & Drugs Administration, the European Medicines Agency, the Australian Therapeutic Goods Administration, the Japan Pharmaceuticals and Medical Devices Agency, and Health Canada.

Other considerations

N/A

Committee recommendations

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 tolerate angiotensin-converting-enzyme inhibitors.

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

Aspirin + atorvastatin + ramipril – rejection – EML

Aspirin + atorvastatin + ramipril **ATC Code: C10BX06**

Proposal

The application proposed the addition of a fixed-dose combination formulation of aspirin + atorvastatin + ramipril to the core list of the EML for the secondary prevention of cardiovascular disease.

Applicant(s)

Dr Oyere Onuma, WHO, Management of Noncommunicable Diseases

WHO technical department

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

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EML/EMLc

EML

Section

12.7 Fixed-dose combinations of cardiovascular medicines (new)

Dose form(s) and strength(s)

Aspirin + atorvastatin + ramipril

Capsule:

100 mg + 20 mg + 2.5 mg; 100 mg + 20 mg + 5 mg; 100 mg + 20 mg + 10 mg;

100 mg + 40 mg + 2.5 mg; 100 mg + 40 mg + 5 mg; 100 mg + 40 mg + 10 mg

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Core/Complementary

Core

Individual/Square box listing

The application proposed a square box listing with therapeutic alternatives limited to:

- aspirin
- dose-equivalent simvastatin
- any dose-equivalent angiotensin-converting enzyme (ACE) inhibitor.

The intention of square box listings is to limit options to alternatives within the same

pharmacological class.

A similar fixed-dose combination (FDC) formulation containing simvastatin instead of atorvastatin is available. This would be a possible alternative under a square box listing for the statin component.

Alternative formulations containing aspirin, atorvastatin or simvastatin, and different ACE inhibitors are not currently available. It may therefore not be appropriate to include a square box against the ACE inhibitor component. FDC formulations containing alternative antihypertensives to ACE inhibitors are available but would not be included as possible alternatives under a square box listing for the ACE inhibitor component.

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

This was the third time an application had been made for inclusion on the EML of an FDC formulation for secondary prevention of cardiovascular disease (CVD). Previous applications were considered by the Expert Committee in 2013 and 2015.

2013

The 2013 application made reference to three FDC formulations of varying combinations and strengths (*1*). It was unclear to the Expert Committee which of the combinations/strengths was being proposed for inclusion in the EML.

The Committee noted that there was a need for access to effective and appropriate secondary prophylaxis for CVDs. Although there is wide acceptance of the concept of using an FDC for the prevention of CVD, the proposal did not present a comprehensive review of the projected health gains from use of any of the FDCs in either primary or secondary prophylaxis.

The clinical trials cited in the proposal were chiefly in primary prevention, were of short duration, and relied on surrogate end-points (*2, 3*). At the time, there was no trial with any of the FDCs that was powered to show a difference in morbidity and mortality. While the medicines in the proposed FDCs had been individually tested, there had been no adequate trials of these combinations in secondary prophylaxis.

The Expert Committee considered that there might be improved adherence to treatment regimens using an FDC as opposed to multiple separate agents. However, the Committee also noted that previous reviews of the effect of FDCs on adherence in other therapeutic areas such as HIV and malaria may not be directly relevant to the potential adherence outcomes in patients with CVD. In addition, there was no evidence to substantiate the claim that widespread use of the proposed FDCs would translate into significant clinical benefits or whether such use would also be associated with increased adverse effects.

The Expert Committee noted serious gaps in the data on the proposed FDC formulations. Only one of the three dosage forms listed had undergone a bioavailability study comparing the individual components with the FDC (*4*). The application stated that "other fixed-dose combination therapies demonstrate similar degrees of bioequivalence with the individual components" but did not provide data to support this claim.

The Expert Committee therefore recommended that these products should not be included in the EML. However, it noted that the use of FDCs for the prevention of CVD is a promising concept and that a further submission should be made once adequate clinical

trials were available and the choice of formulation was clear.

The 2013 application, expert reviews and supporting documents are available at http://www.who.int/selection_medicines/committees/expert/19/applications/polypill/en/

2015

The 2015 application requested inclusion of one or more combination products and proposed listing as a therapeutic group with a square box symbol, allowing use of different combinations and formulations (*5*). The Committee expressed concerns over the practicality of listing a single polypill formulation as the representative of a heterogeneous group, given the large number of different combinations and doses available.

The 2015 application presented data from a 2014 Cochrane review that included nine randomized controlled trials (RCTs) of FDC therapy, containing at least one lipid-lowering medicine and one blood-pressure-lowering medicine for primary and secondary prevention of CVD (*6*). The studies included in the systematic review differed in the composition of the FDCs, the patient populations and the comparison treatment. Three trials compared FDC therapy with usual care; the other six trials compared combination therapy with either active control (e.g. therapeutic lifestyle changes) or placebo. Only one of the included trials, UMPIRE 2013, compared FDC therapy, either (a) aspirin 75 mg + simvastatin 40 mg + lisinopril 10 mg + atenolol 50 mg or (b) aspirin 75 mg + simvastatin 40 mg + lisinopril 10 mg + hydrochlorothiazide 12.5 mg, with multiple individual medications (*7*). Moreover, the reviewers found that five out of the nine trials had a high risk of bias in areas including selection, performance, detection and attrition. The reviewers' conclusions did not favour FDC therapy, as effectiveness in terms of all-cause mortality or cardiovascular events was uncertain.

The Committee noted that the main argument of the application was the potential to improve secondary prevention by improving treatment adherence. In the UMPIRE 2013 trial, adherence was defined as taking aspirin, a statin and two or more blood-pressure-lowering medicines at least four days per week. At 15 months, adherence was 86% in the intervention group compared with 65% in the comparator group (relative risk (RR) of being adherent 1.33; 95% confidence interval (CI) 1.26–1.41) (*7*). Notably, participants randomized to the intervention arm received FDC therapy free of charge whereas participants randomized to usual care were responsible for their own drug costs, which may have led to increased adherence in the FDC arm.

The FOCUS study measured adherence in secondary prevention using a self-reported questionnaire. Patients were randomized to either a polypill (containing aspirin 100 mg + simvastatin 40 mg + and ramipril 2.5, 5 or 10 mg) or the three medicines given separately (usual care). In the intention-to-treat population, after 9 months, 41% in the usual care group and 50.8% in the FDC group were reported to be taking the medication adequately (*8*). However, the study did not identify differences in mean systolic blood pressure, mean low-density lipoprotein (LDL) cholesterol levels, serious adverse events or death between the FDC group and the usual care arm. An FDC feasibility trial in Sri Lanka detected no statistically significant differences between FDC (aspirin 75 mg + simvastatin 20 mg + lisinopril 10 mg and hydrochlorothiazide 12.5 mg) and standard care (not defined) in terms of reductions in systolic blood pressure, total cholesterol or 10-year risk of CVD: more patients in the standard care group completed the study (93% compared with 86% of the

FDC group) (*9*).

A 2012 meta-analysis of RCTs reviewed the evidence for efficacy of FDCs compared with placebo and current care on surrogate outcomes: the FDCs significantly reduced blood pressure and cholesterol. However, the observed reduction in systolic and diastolic blood pressure and in total and LDL cholesterol were often less than would have been expected from the component medications based on trials of these agents taken as single medications (*10*). These results were consistent with the Cochrane review, which also drew attention to a high degree of statistical heterogeneity in comparisons of blood pressure and lipids ($I2 \geq 70\%$) that could not be explained, meaning that these results should be viewed with caution. Data on all-cause mortality and cardiovascular events were limited: mortality and cardiovascular event rates were low in both groups (1.2% in the intervention group compared with 1.0% in the comparator group, and 4.0% rate in the intervention group compared with 2.9% in the comparator group) (*6*).

As in the 2013 application, data from the TIPS-1 and TIPS-2 studies of Polycap were presented in 2015, comparing full-dose treatment (2 x Polycaps plus 30 mEq/L potassium supplement) with half-dose treatment (1 x Polycap) (*3*). Higher-dose treatment was associated with statistically significantly larger reductions in total and LDL cholesterol and in systolic and diastolic blood pressure, with similar tolerability of the two doses (6.9% vs 7.8% discontinuations).

With regard to safety, FDC therapy was associated with modest increases in adverse events compared with placebo, single-drug active component, or usual care (multiple drug therapy) (30% vs 24%; RR 1.19; 95% CI 1.09–1.30) (*6*). This may be associated with improved adherence to a multidrug regimen. Higher rates of discontinuation were reported in participants randomized to FDC in trials than in participants given an active control or placebo (14% vs 11.5%; RR 1.26; 95% CI 1.02–1.55) (*6*). These results were consistent with the meta-analysis by Elley et al. (*10*) and presented limited heterogeneity across studies compared with other outcomes. The UMPIRE 2013 trial showed a higher rate of cardiovascular events in the FDC group (5.0%) than in the usual care group (3.5%), but this was not statistically different. The UMPIRE 2013 trial also reported on health-related quality-of-life measures using the EQ-5D instrument. Mean (standard error) summary index scores were similar in the intervention and comparator groups: 0.82 (0.01) vs 0.81 (0.1), $P = 0.43$ (*7*).

The Committee noted that, although some preliminary evidence suggested improved adherence with FDC formulations, these improvements were limited and unlikely to be associated with relevant differences in clinical outcomes. The Committee was also concerned about the higher rates of adverse events and discontinuations reported in patients randomized to FDC therapy in the trials.

In addition, the Committee expressed concern about the difficulty that would be associated with dose titration or cessation of individual ingredients within the FDC formulations, as is a common occurrence with medicines used for prevention and treatment of CVD.

The Expert Committee acknowledged the potential advantages of FDCs for improving adherence and for providing an affordable product for secondary prevention of CVD. On the basis of the evidence presented in the application for various FDCs, however, the

Committee did not recommend addition of any of the preparations to the EML.

The 2015 application, expert reviews and supporting documents are available at http://www.who.int/selection_medicines/committees/expert/20/applications/aspirin_statin_antihyper_Ad/en/

Public health relevance (burden of disease)

The burden of CVD globally, as a major cause or morbidity and mortality, is well known. In 2012, CVDs were responsible for 17.5 million (31%) global deaths (*11*), with more than 80% of CVD deaths occurring in low- and middle-income countries (*12*). The risk of CVD events has been shown to be greater in people who have had a prior CVD event than in those without prior CVD (*13, 14*).

The Prospective Urban Rural Epidemiology (PURE) study of people with a history of coronary heart disease found that 44% of respondents in high-income countries, 13% in upper-middle-income and 3% in lower-middle-income countries reported taking at least three out of four recommended medicines (antiplatelet medicines, statins, beta-blockers and ACE Inhibitors (or angiotensin receptor blockers (ARBs)) for secondary prevention of CVD (*15*).

Summary of evidence – benefits (from the application)

New evidence in the current application not previously presented in the earlier applications included the results from a prospective meta-analysis of individual patient data of 3140 patients from three trials comparing polypill-based care with usual care (active control) in patients with established CVD or at high risk of CVD (*16*). Polypill formulations used in the study included aspirin, simvastatin and two antihypertensive medicines (lisinopril and atenolol or hydrochlorothiazide). After 12 months, compared with the usual care arm for the primary study end-points, patients in the polypill arm had higher self-reported adherence to combination therapy (80% vs 50%; relative risk (RR) 1.58; 95% CI 1.32–1.90), lower systolic blood pressure (–2.5 mmHg; 95% CI −4.5 to −0.4) and lower LDL-cholesterol (−0.09 mmol/L; 95% CI −0.18 to 0.00). The greatest effects were observed in those patients who were undertreated at baseline.

The primary end-point was self-reported adherence to antiplatelet, statin and at least *two antihypertensive* medicines. For the secondary outcome of self-reported adherence to therapy involving antiplatelet, statin and at least *one antihypertensive* medicine (more closely aligned with the formulation currently proposed for EML inclusion), the polypill arm remained superior to the usual care arm but with a smaller effect size compared with the primary end-point (84% vs 76%; RR 1.11; 95% CI 1.07–1.14).

The current application identified five trials of polypill-based therapy compared with active control in 3080 patients with either established CVD or at high risk of CVD (*7–9, 17, 18*). Of these, three had been previously considered by the Expert Committee (*7–9*). The current application summarized the effectiveness findings for the five trials for adherence, systolic blood pressure, LDL cholesterol, cardiovascular events and acceptability. Results were reported only for patients with established CVD (76%), the target population for the requested EML listing.

When reported, adherence (measured by different methods in the various studies) was

better in the FDC groups than usual-care groups. Only the UMPIRE trial demonstrated a statistically significant difference between FDC and controls for end of trial mean systolic blood pressure and end of trial LDL-cholesterol (*7*). No statistically significant difference was observed between treatment groups for the proportion of patients experiencing a fatal or non-fatal cardiovascular event (*7, 17, 18*). This outcome was not reported in the FOCUS trial. Findings for acceptability are summarized in the application and suggest that FDC therapy is generally acceptable to both patients and health-care providers.

Summary of evidence – harms (from the application)

As previously, the application described safety findings from meta-analyses (*6, 10*). In addition, the current application described safety findings from the five trials noted above. No statistically significant differences in the proportion of patients experiencing at least one serious adverse event were observed (or were not reported) between FDC and control arms. Treatment discontinuations due to adverse events reported in the FOCUS trial were 4% for FDC and for components administered separately (*8*).

Additional evidence (not in the application)

A Public Assessment Report (PAR) of the application made by Ferrer International (manufacturer of Trinomia®) for marketing authorization in Greece, Romania and Sweden is available: https://www.aemps.gob.es/cima/pdfs//ipe/78574/IPE_78574.pdf

The PAR describes a bioequivalence study comparing the FDC with co-administered component monotherapy in healthy adults. The FDC was found to be equivalent to the reference (components) with respect to the extent and rate of absorption based on statistical analysis.

WHO guidelines

The 2007 WHO *Pocket guidelines for assessment and management of cardiovascular risk* (*19*) recommendations for pharmacological treatment for secondary prevention of CVD include aspirin, antihypertensives (beta-blockers, ACE inhibitors, thiazide diuretics) and lipid-lowering therapy with statins.

Similar recommendations are made by Australian, European and USA guidelines (*20–22*).

Costs/Cost–effectiveness

A cost–effectiveness analysis evaluating the health and economic benefits of adherence to FDC therapy for secondary prevention of CVD in the United Kingdom concluded that FDC therapy was a cost-effective strategy for preventing fatal and non-fatal cardiovascular events (*23*). The base case for the model estimated that, over 10 years, FDC therapy would improve adherence by around 20% and prevent 15% of fatal and non-fatal cardiovascular events per 1000 patients compared with multiple-component monotherapy.

A subsequent analysis using an adapted version of the Markov model compared the cost–effectiveness of FDC treatment with multiple-component monotherapy over 10 years (*24*). It estimated that FDC therapy would avoid 46 non-fatal and 11 fatal cardiovascular events

per 1000 patients treated. The number of patients needed to treat with FDC therapy was 22.2 and 45.4 to avoid a non-fatal and fatal cardiovascular event, respectively. The analysis concluded that FDC therapy is a cost-effective treatment strategy.

Upon request from the Secretariat, the applicant provided the following summary of the cost of the FDC compared with the cost of its components:

The FDC (aspirin 100 mg + atorvastatin 20 mg + ramipril 2.5, 5 or 10 mg) has been evaluated for reimbursement in Europe through national health services in Belgium, Greece, Ireland, Portugal and Spain

The ex-factory prices for 1 month's treatment with the FDC, and the total cost of its components in each country, are shown in the table below.

	Belgium	*Greece*	*Ireland*	*Portugal*	*Spain*
Trinomia AAR 100/20/2.5 mg, 28 capsules					
Sum mono-components	€7.14	€16.88	€9.07	€8.88	€8.37
Approved	€8.37	€8.21	€8.37	€8.37	€8.37
Trinomia AAR 100/20/5 mg, 28 capsules					
Sum mono-components	€8.60	€18.12	€9.83	€9.49	€9.87
Approved	€9.87	€9.68	€9.87	€9.87	€9.87
Trinomia 100/20/10 mg, 28 capsules					
Sum mono-components	€11.84	€19.21	€11.0	€12.71	€12.97
Approved	€12.97	€12.72	€12.97	€12.97	€12.97

Availability

This formulation is produced by Ferrer Internacional S.A., Spain

Other considerations

The Expert Committee noted differences between the use of FDC therapies for treatment of communicable diseases and noncommunicable diseases (NCDs). The Committee also noted that pharmacological management of NCDs is complex: it is designed to treat the multiple conditions that a patient might have, must be tailored to the patient's clinical condition, and may require regular adjustments in dosage and schedule of individual components to maximize efficacy and minimize adverse effects. FDCs for communicable diseases (e.g. HIV/AIDS, tuberculosis, malaria, hepatitis C), are designed to target a specific, identified infectious agent and to minimize the development of resistance. Combination therapy is often essential in these conditions and components should not be given individually; less flexibility in doses and components is thus required in tailoring therapy

for individual patients.

The Expert Committee considered that FDCs for NCDs may have advantages over the single medicines given concomitantly, including increased adherence and reduced pill burden. For this reason, the Committee recognized the potential value of FDCs of currently listed essential medicines, with regulatory approval and demonstrated bioavailability, for the management of chronic NCDs. However, the Committee considered that many different combinations of cardiovascular medicines exist, with multiple permutations of components from different therapeutic classes, varying strengths and dosages. The Committee noted, for example, that at least 14 different combination products are currently in development (*25*), and that there does not yet appear to be consensus on the optimal components for a "universal FDC". The Committee also agreed that there is a need to develop the evidence base for FDCs in low- and middle-income countries, including procurement, utilization, cost–effectiveness and adherence (*26*).

Given this complexity, the Committee was firmly of the view that it would not be appropriate to list individual FDCs for NCDs on the EML as this would not provide the required flexibility for choosing optimal combinations and doses of multidrug therapy for cardiovascular disease. However, the Committee also recognized that, particularly for patients on established multi–medicine regimens, moving to an FDC containing the same products would probably improve adherence and that there should therefore be discretion at national level in making this choice.

Committee recommendations

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 that the existing WHO guidance documents on FDCs urgently need updating, 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.

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Section 15: Disinfectants and antiseptics

15.1: Antiseptics

Hypochlorous acid – rejection – EML and EMLc

Hypochlorous acid (sodium hypochlorite) **ATC Code: DO8AX07**

Proposal

The application requested addition of hypochlorous acid solution and hydrogel to the EML and EMLc for use in wound management. The solution is intended for use as a topical wound disinfectant, while the hydrogel is intended to be applied topically with dressings as part of moist wound healing practices.

Applicant(s)

Te Arai BioFarma Limited

WHO technical department

WHO Department of Infection Prevention and Control

EML/EMLc

EML and EMLc

Section

15.1 Antiseptics

Dose form(s) and strength(s)

Solution: containing 30 ppm hypochlorous acid, 40 ppm sodium hypochlorite, sodium chloride plus other oxidative species

Hydrogel: containing 80 ppm hypochlorous acid, 20 ppm sodium hypochlorite, sodium chloride, sodium magnesium fluorosilicate, sodium phosphate plus other oxidative species

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Core/Complementary

Core

Individual/Square box listing

Individual

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

Currently, the EML includes chlorhexidine, ethanol and povidone iodine as topical antiseptics.

The EML does not currently include any basic or specialized wound dressings or other topical products for use in moist wound healing practices.

Public health relevance (burden of disease)

Chronic wounds and the infections associated with them are the source of considerable morbidity and health-care costs. They more commonly affect older patients (>60 years) and, with an ageing population, the prevalence can be expected to increase. Topical antibiotics are generally not recommended in the management of chronic wounds, and systemic antibiotics are indicated only in particular circumstances (e.g. systemic sepsis, cellulitis) (*1*). The use of topical biocides is a preventive control measure against the spread of nosocomial infections and multidrug-resistant bacteria within hospitals and other health-care and community settings.

Summary of evidence – benefits (from the application)

The application presented results from 17 randomized and non-randomized trials in support of the efficacy of hypochlorous acid versus various comparators in the management of different infectious wound types, including diabetic foot ulcers, chronic wounds, postoperative wounds and peritonitis (*2–18*). The quality of the studies was not assessed, but there appeared to be considerable heterogeneity in terms of interventions, comparators and outcomes measured. No systematic-reviews were identified or conducted.

Overall, the studies appeared to show better efficacy for hydrochlorous acid solution compared with other treatments for outcomes including wound size, purulent discharge, appearance of granulation and epithelization, length of hospital stay, and signs of infection.

Most of the studies involved hypochlorous acid solution and provided no information about the hydrogel formulation.

The 2016 guidelines of the International Wound Infection Institute note that super-oxidized solutions of hypochlorous acid and sodium hypochlorite are claimed to disrupt biofilm and kill planktonic bacteria while being safe for the wound and the patient (*19*).

Summary of evidence – harms (from the application)

he application provided limited information regarding the safety of hypochlorous acid solution in clinical use. It stated that hypochlorous acid solution does not target cell nuclei, produces only limited damage to cell membranes, and does not induce DNA oxidation or accelerated ageing.

A randomized controlled trial (RCT) of 45 patients with infected diabetic foot ulcers treated with “neutral pH super oxidized aqueous solution” (NpHSS) or standard care found NpHSS to be associated with less cytotoxicity and less damage to granulating tissue and surrounding healthy tissue (*7*). An RCT of 40 patients with postsurgical lesions

of the infected diabetic foot treated with a stable super-oxidized solution with neutral pH or povidone iodine found no difference in adverse events between groups; however, frequency of reinfection was higher in the povidone iodine group (*18*).

Additional evidence (not in the application)

N/A

WHO guidelines

The application stated that hypochlorous acid solution and hydrogel are included in the 2015 Antibiotic Guidelines of the Cook Islands and Western Samoa; WHO support for their preparation is acknowledged. The guidelines were not referenced in the application, nor were copies available for review.

Costs/Cost–effectiveness

The pricing of hypochlorous acid solution proposed by the applicant is US$ 5.52/500 mL (equivalent to US$ 0.011/mL). In comparison, the median price for povidone iodine 10% solution according to the MSH International Drug Price Indicator Guide is US$ 0.0087/mL (*20*). Prices of povidone iodine 10% quoted in the application range from US$ 0.0134/mL (Fiji) to US$ 0.0946/mL (Australia).

The pricing of hypochlorous acid hydrogel proposed by the applicant is US$ 6.00/250 g (equivalent to US$ 0.024/g). Comparator prices for alternative hydrogels are quoted as ranging from US$ 0.1927/mL to US$ 0.452/mL.

Availability

The application stated that hypochlorous acid solution is available under the trade names Electromicyn, Microcyn, Dermacyn, MicroSafe, Microdacyn and Oxum throughout the Americas and in Asia, Europe, India, the Middle East and the Pacific Islands.

Other considerations

The Expert Committee noted that the product was classified by regulatory agencies in some countries (e.g. Australian Therapeutic Goods Administration, European Medicines Agency, U.S. Food & Drug Administration) as a Class IIb Medical Device, as a product that comes into contact with injured skin and with an intended purpose of healing the breached dermis by ancillary effects.

Committee recommendations

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.

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Section 18: Hormones, other endocrine medicines and contraceptives

18.3: Contraceptives

18.3.1: Oral hormonal contraceptives

Ulipristal acetate – addition – EML

Ulipristal acetate **ATC Code: G03AD02**

Proposal

The application requested 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.

Applicant(s)

HRA Pharma

WHO technical department

The WHO Department of Reproductive Health and Research stated its support for inclusion of this medicine on the EML for emergency contraception in alignment with current WHO guidelines.

EML/EMLc

EML

Section

18.3.1. Oral hormonal contraceptives

Dose form(s) and strength(s)

Tablet: 30 mg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Currently, levonorgestrel (LNG-EC) is included on the EML for use as an emergency oral hormonal contraceptive.

Public health relevance (burden of disease)

Target 3.7 of the Sustainable Development Goals is to ensure, by 2030, universal access to sexual and reproductive health-care services, including family planning, information and education, and the integration of reproductive health into national strategies and programmes (*1*).

In 2012, it was estimated that more than 85 million of pregnancies were unintended, representing approximately 40% of all pregnancies. Of these, 50% ended in abortion, 13% in miscarriage and 38% in an unplanned birth (*2*). In developing countries, it corresponds to 74 million unintended pregnancies as a consequence of the lack of use of effective methods of regular contraception (70%) and contraceptive failure (30%) (e.g. missed pills, broken or slipped condoms) (*3, 4*). In 2016, of the 20 million pregnancies occurring in adolescents aged 15–19 years living in developing countries, approximately 50% were unintended (*5*). Maternal causes are the second highest ranked source of mortality in this age group globally (*6*).

In developing countries, the current use of emergency contraception (EC) is relatively low. Among sexually active women, only 3% reported having ever used EC (7).

Unintended pregnancies are usually associated with negative health, financial, social and emotional consequences. In 2012, about 50% of unintended pregnancies ended in induced abortion (*2*). In 2003, an estimated 42 million pregnancies were voluntarily terminated, 20 million unsafely, endangering health and life.

Summary of evidence – benefits (from the application)

The application presented the results of a 2012 systematic review (*8*) that included two high-quality randomized controlled trials (RCTs) comparing ulipristal acetate (UPA) and LNG in 1716 women with regular menses who requested EC following unprotected intercourse (*9, 10*). Both RCTs were determined to have a low risk of bias.

The results showed that UPA-EC was significantly more effective in preventing pregnancy than LNG-EC (risk ratio (RR) 0.58; 95% confidence interval (CI) 0.35–0.99; $P = 0.04$). For use within 72 hours of unprotected sexual intercourse, UPA-EC was shown to be more effective, although the difference was only marginally significant (RR 0.63; 95% CI 0.37–1.07; $P = 0.089$) (*8*).

In a meta-analysis that used a logistic-regression model, which took into account known confounding factors that may alter the treatment effect, the odds of pregnancy were significantly lower ($P < 0.05$) among women who used UPA-EC than those who used LNG-EC, taken within 24, 72 and 120 hours of unprotected intercourse (*9*).

Results from a pooled analysis of three pharmacodynamic studies in which EC treatment was given at a late follicular stage (follicle ≥18 mm diameter) showed that UPA-EC was significantly better than LNG-EC (1.5 mg) at delaying follicular rupture by 5 days, whether treatment was given before the luteinizing hormone (LH) surge (RR 4; 95% CI 1.5–10.7; $P = 0.0026$) or after the LH surge but before the LH peak (RR 55.5; 95% CI 1.5–20.4; $P = 0.0018$). No treatment was effective at postponing follicular rupture when given at the time of the LH peak (*11*).

Efficacy in obese patients

Pooled data from two RCTs comparing UPA-EC and LNG-EC assessed risk of pregnancy in women categorized by body mass index (BMI) (*12*). Results showed that pregnancy risk was doubled in overweight women who took LNG-EC in comparison with normal or underweight women (odds ratio (OR) 2.09; 95% CI 0.86–4.87; not significant), and was more than 4 times greater in obese women (OR 4.41; 95% CI 2.05–9.44; $P = 0.0002$). Among the women who took UPA-EC, the risk of pregnancy in overweight women did not differ from that for women with BMI <25 kg/m^2 (OR 0.97; 95% CI 0.27–2.83; not significant) and the risk of pregnancy in obese women who took UPA-EC was higher but not significantly so (OR 2.62; 95% CI 0.89–7.00; not significant).

Efficacy in adolescent patients

As part of the Paediatric Investigation Plan agreed with the European Medicines Agency (EMA), a post-marketing phase IV observational study was conducted with the objective of assessing safety, tolerability and efficacy of UPA-EC in postmenarcheal adolescent girls and adult women. Of the 579 women included, 279 were under 18 years of age (of whom 76 were under 16 years). In the efficacy-analysis population, pregnancy occurred in seven women (of whom two were under 16 years), yielding a pregnancy rate 1.5%, similar to that observed in adult women (*13*).

Summary of evidence – harms (from the application)

Safety data from a comparison of adverse events (AEs) following treatment with UPA-EC (n = 1879) and LNG-EC (n = 1891) showed no differences between the two treatments. The most frequent AEs were nausea, vomiting, breast tenderness, headache, dizziness, fatigue, abdominal pain, diarrhoea, spotting/bleeding after treatment, dysmenorrhoea and back pain (*8*).

Post-marketing experience (1.4 million women) and a meta-analysis of phase III RCTs (2221 women) reported only two serious AEs potentially related to UPA-EC use (dizziness and fainting). No increased risk of venous thromboembolic events was identified (*9, 14, 15*).

A prospective, observational, multicentre study assessed the safety profile in adolescents under 18 years old (*13*). The most frequent AEs were headache, nausea and abdominal pain, changes in cycle duration and menorrhagia. These data indicate that the safety profile observed in adolescents is similar to that observed in adults.

Safety and tolerability of repeated use of UPA-EC within the same menstrual cycle were assessed. Most frequent AEs were headache, nasopharyngitis, influenza and mild anaemia. All were of mild or moderate intensity. No serious AEs were reported (*16*).

Additional evidence (not in the application)

N/A

WHO guidelines

UPA-EC is included in the WHO *Medical eligibility criteria for contraceptive use* (*17*).

Costs/Cost–effectiveness

UPA-EC costs between €15–57 in Europe and US$ 40–70 in USA. The manufacturer, HRA Pharma, has proposed tiered pricing strategies to provide sustainable and affordable access.

The cost–effectiveness of UPA-EC compared with LNG-EC for the avoidance of unintended pregnancy has been analysed in several studies (*18–22*). Potential cost-savings have been identified in several cases; in the United Kingdom, for example, the additional cost to prevent one pregnancy by giving UPA-EC rather than LNG-EC was calculated to be £311, which is lower than the cost of an unintended pregnancy (£948), regardless of the outcome (*19*).

Availability

Currently, UPA is marketed in 65 countries (19 countries of low- or lower-middle income) and is available without prescription in about 40 countries, including the European Union where it was approved by EMA in 2014.

Other considerations

Preventing unintended pregnancy and reducing adolescent childbearing through universal access to sexual and reproductive health-care services are critical to further advances in the health of women, children and adolescents.

Committee recommendations

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.

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18.3.2:Injectable hormonal contraceptives

Medroxyprogesterone acetate – change: new formulation and strength – EML

Medroxyprogesterone acetate **ATC Code: G03AC06**

Proposal

The application requested the addition of a new formulation of subcutaneously-administered depot medroxyprogesterone acetate to the core list of the EML as an injectable hormonal contraceptive.

The application also requested an amendment to the current EML listing of depot medroxyprogesterone acetate to clarify that its route of administration is intramuscular.

Applicant(s)

Pfizer Limited

WHO technical department

The WHO Department of Reproductive Health and Research stated its support for inclusion of this formulation on the EML for contraception in alignment with current WHO guidelines.

EML/EMLc

EML

Section

18.3.2 Injectable hormonal contraceptives

Dose form(s) and strength(s)

Injection (subcutaneous): 104 mg/0.65 mL in pre-filled syringe or injection delivery system

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Core/Complementary

Core

Individual/Square box listing

Individual

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

Depot medroxyprogesterone acetate (DPMA) for IM injection (150 mg/mL) has been included on the EML since 1985, initially on the Complementary List and then moved to the core list in 2005.

Public health relevance (burden of disease)

Estimates have indicated that contraceptive use contributes to reduced maternal mortality and morbidity. In an analysis of 172 countries, contraceptive use was estimated to have reduced maternal mortality by 44%, thereby averting 272 040 maternal deaths (*1*). A significant unmet need for contraception exists, with an estimated 222 million women in low-income countries lacking access (*2*). Addressing this unmet need may avert a further 30% of maternal deaths (*3*).

Summary of evidence – benefits (from the application)

Evidence for the clinical effectiveness of medroxyprogesterone acetate was evaluated at the time of listing.

The application presented the results of two phase 3, open-label, non-comparative, multinational 1-year studies which assessed the efficacy and safety of subcutaneous DMPA (DMPA-SC) (*4*). In each study, participants received contraceptive injection every 3 months for up to 1 year. The combined total was 16 023 woman-cycles of exposure. No unintended pregnancies were reported in either study. Both the Pearl Index (number of pregnancies per 100 woman-years of use) and the cumulative pregnancy rate at 1 year (the primary end-point) were 0 (95% confidence intervals not calculated as no pregnancies were reported).

A small comparative study in 58 women assessed efficacy, ovulation suppression and return to ovulation at 12 months after a single dose of DMPA-SC or DMPA-IM (*5*). Pharmacokinetic parameters of the SC formulation were also assessed. Results indicated that suppression of ovulation was immediate following single-dose SC administration. DMPA-SC consistently suppressed ovulation for the 13-week dosing interval, with the earliest return to ovulation occurring at 15 weeks. Median time to return to ovulation was 30 weeks. The cumulative rate of ovulation at 12 months post-injection (the primary efficacy end-point) was 97.4% and 94.7% in the SC and IM groups, respectively. Suppression of ovulation did not appear to be affected by body mass index or race.

Summary of evidence – harms (from the application)

Evidence for the safety of medroxyprogesterone acetate was evaluated at the time of its original listing.

The overall safety profile of DMPA-SC is consistent in most respects with that of DMPA-IM and reflects the known physiological effects of medroxyprogesterone acetate. With the exception of injection site reactions, the types of adverse events seen with DMPA-SC are similar to those with DMPA-IM and include bleeding irregularities, amenorrhoea, weight gain, headache and mild, reversible loss of bone mineral density. A higher rate of injection site reactions was observed in patients receiving DMPA-SC (*4*).

Additional evidence (not in the application)

A systematic review of 14 studies investigated the safety of DMPA-SC in women with various characteristics or medical conditions (*6*). The review found evidence to support DMPA-SC as a safe contraceptive treatment for use by women with conditions and characteristics

that included age, obesity, endometriosis and HIV infection. The review also found that the two formulations appear to be therapeutically equivalent when used by healthy women.

WHO guidelines

The WHO *Medical eligibility criteria for contraceptive use* (*7*) states that DMPA-IM and DMPA-SC appear therapeutically equivalent, demonstrating similar pharmacokinetics, effects on serum estradiol levels and high contraceptive efficacy. It recommends that all guidance for DMPA-SC should follow the current recommendations for DMPA-IM (very low-quality evidence).

Costs/Cost–effectiveness

The unit price for DMPA-SC is US$ 1 to qualified purchasers in 69 of the world's poorest countries with a partnership consortium. For populations and countries not included in the agreement, prices are based on a differential pricing structure and take into consideration the local economic conditions and family planning climates.

In comparison, the median supplier price of DMPA-IM, according to the International Medical Products Price Guide, is US$ 0.75 per unit (*8*).

Availability

Pfizer Ltd.

Other considerations

Comments on the application received from Médecins Sans Frontières (MSF) indicated that the organization did not support addition of this SC formulation to the EML, based on an anticipated low probability of programmes involving self-administration and the additional cost in resource-limited settings compared with the IM formulation.

Committee recommendations

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.

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18.5: Insulins and other medicines used for diabetes

Long-acting insulin analogues – rejection – EML and EMLc

Insulin glargine	**ATC Code: A10AE04**
Insulin detemir	**ATC Code: A10AE05**

Proposal

The application proposed the addition of long-acting insulin analogues as a pharmacological class to the core list of the EML and EMLc for treatment of type 1 diabetes in adults, adolescents and children aged 2 years and above. As there is more evidence for its effectiveness and safety, it was proposed that insulin glargine be listed with a square box as representative of the class, with alternatives limited to insulin detemir and biosimilar insulin glargine (Basaglar).

Applicant(s)

Huda M. Ashoor, Jesmin Antony, Dr Wanrudee Isaranuwatchai, Dr Areti Angeliki Veroniki, Dr Sharon E. Straus, Dr Andrea C. Tricco, Knowledge Translation Program, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada

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WHO technical department

WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

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EML/EMLc

EML and EMLc

Section

18.5 Insulins and other medicines used for diabetes

Dose form(s) and strength(s)

All insulins are supplied dissolved or suspended in liquids. The standard and most commonly used strength in most countries is U-100, which means its insulin content is 100 units/mL.

Core/Complementary

Core

Individual/Square box listing

Insulin glargine listed with a square box, with alternatives limited to insulin detemir and biosimilar insulin glargine (Basaglar).

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

In 1982 the U.S. Food & Drugs Administration (FDA) approved human insulin produced using gene technology, as a substitute for chromatographic purification techniques of highly purified animal insulin. In 1985 the Expert Committee approved the inclusion on the EML of isophane NPH (neutral protamine Hagedorn) insulin. Since 1996, various insulin analogues, altered forms of human insulins, with different pharmacokinetic characteristics (absorption, distribution, metabolism, excretion), have been introduced worldwide. Today, several rapid- and long-acting insulin analogues are available (e.g. Humalog, Lilly; Lantus and Apidra, Aventis; Levemir and NovoRapid, Novo Nordisk). In 2011 the Expert Committee reviewed insulin analogues. At that time evidence was judged of to be of low or very low quality and the cost–effectiveness profile to be uncertain. Since that time, additional evidence has become available.

Public health relevance (burden of disease)

Diabetes and its complications are among the leading causes of premature mortality; 3.7 million deaths were reported in 2012 (*1*). Globally, the prevalence of diabetes has almost doubled since 1980 (*1*) and accounts for 14.5% of all-cause mortality in people aged 20–79 years, with the number of cases of type 1 diabetes rising by 3% each year (*2*). If current trends continue, it is estimated that 642 million people will be living with diabetes by 2040 (*2*). Currently, type 1 diabetes cannot be prevented; however, it can be managed with a combination of interventions including dietary changes, physical activity, and medication to help control blood glucose levels.

All people living with type 1 diabetes need insulin, as do more than 10% of people with type 2 diabetes (*3*).

Summary of evidence – benefits (from the application)

The evidence presented was based on a systematic review and network meta-analysis that examined the comparative safety, effectiveness and cost–effectiveness of the long-acting insulin products glargine and detemir compared with intermediate-acting insulin in patients with type 1 diabetes (*4, 5*). A total of 38 relevant studies and one companion report were included in the review, including 27 randomized controlled trials (RCTs) involving 7496 patients.

Glycated haemoglobin (HbA1c) was the primary outcome. Once-daily glargine and detemir both produced a statistically significantly reduction in HbA1c compared with once-daily NPH: mean difference for glargine –0.5 (95% confidence interval (CI) –0.87 to –0.13) and for detemir –0.16 (95% CI –0.3, –0.03) (low quality of evidence). When compared with NPH twice or more daily, the insulin analogues were not associated with a reduction in HbA1c. In a subgroup analysis by baseline HbA1c, once-daily glargine and detemir were found to be statistically significantly more effective than once-daily NPH for patients with poorly controlled diabetes (HbA1c >8%). The decrease in HbA1c showed no difference between glargine and detemir (low to moderate quality of evidence).

For weight gain, patients receiving detemir once or twice daily experienced significantly less weight gain than those receiving NPH once or twice daily daily (moderate quality

evidence). Significantly less weight gain was also experienced by patients receiving glargine once daily compared with than those receiving NPH once or twice daily; and by patients receiving detemir once daily compared with those receiving NPH daily (low-quality evidence).

For serious hyperglycaemia, retinopathy, transient ischaemic attack, death due to myocardial infarction, death due to cardiopulmonary arrest, all-cause mortality, pancreatic cancer, uterine cancer and quality of life, direct comparison meta-analyses comparing glargine and detemir with NPH did not reached statistical significance.

Summary of evidence – harms (from the application)

Insulins are hypoglycaemia-inducing agents. There is evidence that hypoglycaemia may adversely affect the cardiovascular risk profile, particularly in older people and in patients affected by diabetes of longer duration (*6*). Overall, published trials show that severe hypoglycaemia may increase cardiovascular mortality (*7, 8*). Preventing hypoglycaemia is as least as important for disease management and long-term prognosis as tight glycaemic control.

Evidence for safety was based on the systematic review and network meta-analysis cited above (*5*). Significantly fewer episodes of severe hypoglycaemia were experienced by patients receiving detemir once or twice daily compared with those given NPH once or twice daily (odds ratio (OR) 0.62; 95% CI 0.42–0.91). In one RCT, glargine once daily was associated with a statistically significant increase in episodes of severe hypoglycaemia compared with detemir once or twice daily (OR 4.30; 95% CI 1.19–15.53). In the network meta-analysis, however, these findings were no longer statistically significant.

Additional evidence (not in the application)

N/A

WHO guidelines

WHO guidelines on hypoglycaemic agents, including insulin analogues, are currently being developed. The application referred to other systematic reviews and guidelines in addition to the network meta-analysis.

Four previous systematic reviews, published between 2007 and 2011, compared the safety and effectiveness of long-acting insulin analogues with intermediate-acting insulin in patients with type 1 diabetes (*9–12*). For the outcome of HbA1c, two reviews (*10, 12*) concluded that long-acting insulins are probably slightly superior to intermediate-acting insulin. In a network analysis, however, no statistically significant difference was found between the insulin groups (*11*). Heterogeneity prevented the pooling of studies in a 2007 systematic review for this outcome (*9*). One of the reviews (*12*) found that long-acting insulin was associated with a statistically significant reduction in the risk of severe hypoglycaemia when compared with NPH; the other three reviews (*9–11*) found no statistically significant differences between the groups for this outcome.

A recent clinical guideline commissioned by the National Institute for Health and Care Excellence (NICE) presented recommendations based on similar evidence (*13*). The

guideline's network meta-analysis also found long-acting insulin to be statistically significantly more effective in reducing A1c than intermediate-acting insulin and reported a clinically important benefit of long-acting insulin over NPH with respect to severe hypoglycaemia and body weight reduction.

Costs/Cost–effectiveness

In total, 10 studies were included, focusing on three comparisons: glargine vs NPH, detemir vs NPH, and glargine vs detemir.

Comparison between glargine and NPH was reported in eight cost–effectiveness analyses in five studies (*14–18*). Glargine was less costly and more effective in two (*18*) of these analyses for both outcomes of life-years and quality-adjusted life-years (QALYs); these results came from a study that reported receiving financial contributions from Sanofi-Aventis. Of the six analyses (*14, 15, 17, 18*) that found glargine to be both more expensive and more effective than NPH, one study received funding from Health Canada and two from Sanofi-Aventis. The two analyses reporting glargine to be a dominant option were conducted in Germany, whereas the other six analyses were conducted in Canada, Switzerland and United Kingdom.

Five studies (*14, 19–22*) reported on comparisons between detemir and NPH in 14 cost-–effectiveness analyses; one of the five studies was funded by Health Canada and the other four by Novo Nordisk. Three of the analyses found that detemir was less costly and more effective in one of the studies that received funding from Novo Nordisk; the remaining analyses found that detemir was more effective than NPH but that it was more expensive. The three analyses reporting detemir to be a dominant option over NPH came from one international study (*19*) conducted in five European countries with QALY as an outcome from the third-party payer's perspective.

From a societal perspective, one study that received an unrestricted grant from Novo Nordisk found glargine to be less costly and less effective (in terms of both life years and QALYs) than detemir (*23*).

Insulin was found to be 2.5–45 times more expensive than medicines for other noncommunicable diseases (*3*). In USA, the annual cost of insulin for each patient was US$ 736 in 2013 – a threefold increase since 2002. Diabetes medicines are the second most expensive category of prescription drugs in the USA and a huge burden to health budgets (*24*).

Availability

Lack of access to affordable insulin is a global problem: more than half of the people who need insulin are unable to afford or access it, which leads to health complications and early death (*1, 3*). Since lack of access to insulin is a global issue, providing access to affordable essential medicines is one of the items on the 2030 Agenda for Sustainable Development for the World Health Organization (WHO) and its Member States (*1*).

Long-acting insulin analogues are licensed globally for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. Patent protection of these analogues is expiring, or will soon expire, in USA, Europe and elsewhere, and there is

increasing interest in the potential of basal or long-acting biosimilar insulins.

In 2014, the European Medicines Agency approved Abasaglar® as a biosimilar of the reference medicine insulin glargine. In 2015 Basaglar® was approved by the FDA as a follow-on biological of insulin glargine treatment. Copies of the long-acting insulin glargine have been approved and introduced into the market in several countries, including China, India, Kenya, Mexico and Pakistan.

Other considerations

Long-acting insulin appeared to be more expensive than intermediate-acting insulin; however, the application reported instances of long-acting insulin being the cheaper of the two. Most importantly, if the price of long-acting insulins were to fall, the probability that they will be cost effective compared with NPH may increase (*25*). When biosimilar erythropoietins were approved, the price declined by 20% in a relatively short period of time (3 years) (*26*); other studies report a total decline of 30–40% (*27*). Biosimilar insulins have the potential to reduce treatment costs and thus improve access for patients, physicians and health-care systems.

Committee recommendations

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.

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

Second-line treatments for type 2 diabetes:

Sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors

Glucagon-like peptide-1 agonists, basal insulins, bolus insulins and biphasic insulins

ATC Code: see supplementary tables

Proposal

The application proposed updating of section 18.5 Insulins and other medicines used for diabetes of the EML and EMLc with a comprehensive and comparative assessment of all available second-line therapies (to be used in combination with metformin) for treatment of type 2 diabetes in adults, adolescents and children: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 agonists, basal insulins, bolus insulins, and biphasic insulins, including analogues.

Applicant(s)

George A. Wells, Shannon Kelly, Amy Johnston, Shuching Hsieh, Jesse Elliott, Zemin Bai, Li Chen, Alomgir Hossain, Becky Skidmore, Methods and Applications Group for Indirect Treatment Comparisons (MAGIC), Ottawa, Canada; Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario.

Other contributors: Bradley Mitchelmore, Sumeet Singh, Mohammed Jabr, Hongbo Yuan, Melissa Severn, Brendan McIntosh, Karen Lee, Brent Fraser, Julia Lowe, Marshall Dahl.

WHO technical department

WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

EML/EMLc

EML and EMLc

Section

18.5 Insulins and other medicines used for diabetes

Dose form(s) and strength(s)

See tables

Core/Complementary

Core

Individual/Square box listing

The intention of square box listings is to limit options to alternatives within the same pharmacological class. Most medicines for diabetes can be listed under square box.

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

In 2013, the Expert Committee evaluated evidence comparing four groups of oral hypoglycaemics against metformin (biguanide) and sulfonylureas (*1*):

- dipeptidyl peptidase-4 (DPP-4) inhibitors
- thiazolidinediones (TZDs)
- alpha-glucosidase inhibitors, such as acarbose
- meglitinides.

The results from the 2013 review indicated that there were no apparent differences in efficacy across drug classes, and that sulfonylureas were the most cost-effective treatment option. Based on these analyses, the Expert Committee recommended that "there was insufficient evidence to show that any of the medicines in the four groups (DPP-4 inhibitors, alpha-glucosidase inhibitors, meglitinides, or thiazolidinediones) offered any efficacy or safety advantages over the existing medicines [i.e. metformin first-line and sulfonylurea second-line] included in the EML".

Since then, a new drug class has entered the market in several countries for the treatment of patients with type 2 diabetes (T2D) — sodium-glucose cotransporter-2 (SGLT-2) inhibitors. In addition, a fourth DPP-4 inhibitor (alogliptin) and a third glucagon-like peptide 1 (GLP-1) agonist (dulaglutide) have appeared, and new data have been published on the impact on cardiovascular outcomes of some of the new drugs (e.g. GLP-1 agonists, DDP-4 inhibitors and SGLT-2 inhibitors).

Given the newer agents recently approved in most countries and additional evidence from randomized controlled trial (RCTs) published over the past 5 years for the existing and newer agents, there is a need to revisit comparative efficacy, safety and cost.

The comparative assessment in the application was based on an update of a previous CADTH (Canadian Agency for Drugs and Technologies in Health) systematic review and network meta-analyses of second-line therapies for T2D (*2*). In addition, the application reviewed pharmacological treatments for patients with T2D who are at high risk for cardiovascular events. Third-line therapies were not assessed.

Public health relevance (burden of disease)

The worldwide prevalence of diabetes has nearly quadrupled since 1980, rising from 108 million to 422 million in the adult population – and rising faster in low- and middle-income countries than in high-income countries (*3*). This trend is associated with an increase in associated risk factors such as overweight and obesity. In 2012, diabetes caused 1.5 million deaths. Another 2.2 million deaths were caused by higher than optimal blood glucose,

which increases the risks of cardiovascular and other diseases.

Since it is very difficult to distinguish between type 1 diabetes (which requires insulin injections for survival) and type 2 diabetes (in which the body cannot properly use the insulin it produces), separate morbidity data for type 1 and 2 are not available at global or country level. However, most people with diabetes are affected by T2D.

WHO's *Package of essential noncommunicable (pen) disease interventions for primary health care in low-resource settings* provides advice on recommended treatments for diabetes (*4*). The guidance document is out of date, however, and is scheduled for updating in 2017. Current WHO guidelines recommend initiation of pharmacological treatment with metformin monotherapy if a target glycated haemoglobin (HbA1c) level is not reached. Most people with T2D will require continuous pharmacological treatment in order to maintain normal or near-normal glycaemic targets, and blood glucose levels may continue to rise gradually over the course of an individual's life. When initial therapy with lifestyle interventions and metformin monotherapy is unsuccessful, a second oral agent (sulfonylurea) is recommended. This is referred to as second-line therapy or the intensification phase of therapy (i.e. between the initial therapy with metformin and any treatment combination containing insulin).

Historically, insulin or sulfonylureas have been preferred the second-line agents because of efficacy, side-effect profiles, long-term safety and relative cost. However, a number of other agents are available that can be used in combination with metformin: meglitinides, alpha-glucosidase inhibitors, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, basal insulins, bolus insulins, and biphasic insulins. Some of these agents have recently been approved globally (e.g. DPP-4, SGLT-2 inhibitors, GLP-1 agonists).

Summary of evidence – benefits (from the application)

The application summarized results that answer two specific research questions:

1. For adults with type 2 diabetes on metformin monotherapy with inadequate glycaemic control, what is the comparative efficacy and safety of using a drug from one of the following classes as second-line agent:
   - sulfonylurea
   - insulin
   - DPP-4 inhibitor
   - GLP-1 agonist
   - SGLT-2 inhibitor?
2. For adults with type 2 diabetes, what are the comparative cardiovascular effects of drugs belonging to one of the following classes
   - insulin
   - DPP-4 inhibitor
   - GLP-1 agonist
   - SGLT-2 inhibitor?

Question 1: Patients inadequately controlled on metformin

For the first research question, 175 unique RCTs and 78 companion publications were

included in the systematic review. A total of 166 RCTs reported study outcomes of interest. References are reported in the original application.

Treatment history before randomization was poorly reported and often unspecified. Patients using a variety of oral antidiabetic drugs often underwent a run-in period with metformin monotherapy upon trial entry, and were randomized to add-on therapy if glycaemic control was inadequate at the end of the run-in period. No studies assessed the effects of switching from metformin to another antidiabetic drug because of intolerable adverse effects, development of contraindications, or inadequate glycaemic control. Patients with T2D had a variety of co-morbid conditions. Some RCTs targeted subgroups of T2D patients (e.g. those with microalbuminuria, metabolic disorder, dyslipidaemia) or specific populations (e.g. women, Caucasians, or patients in a specific geographical area).

Risk of bias was assessed for all studies using the Cochrane Collaboration's Risk of Bias tool. Included RCTs generally had a moderate risk of bias. RCTs commonly failed to adequately report their methods for random sequence generation and allocation concealment. At least 20% of the studies were assessed to be at high risk of bias due to incomplete reporting of efficacy or safety outcomes.

Overall assessment of the internal and external validity of the included RCTs noted limitations in several areas that have been highlighted in previous CADTH therapeutic reviews. This included the use of surrogate end-points (e.g. HbA1c) rather than more clinically meaningful end-points, limited sample sizes, and duration of follow-up. Many RCTs failed to register in a trial registry (such as Clinicaltrials.gov) or to publish a study protocol.

Poor reporting was a common issue across trials. Failure to report protocol definitions for study outcomes (e.g. hypoglycaemia), true intention-to-treat analyses (i.e. an analysis including all randomized patients), and dose and/or duration of stable metformin therapy before randomization. Many studies failed to adequately report details about the dosage of metformin background therapy during treatment.

Network meta-analyses (NMAs) were conducted for 18 outcomes for the reference case of class comparisons. The full results for all class comparisons, as well as model diagnostics for the fixed and random effects models, are presented in the appendices to the application.

For each outcome, the mean differences or odds ratios from the NMA of the reference case are provided, comparing each drug class added on to metformin background therapy with metformin monotherapy. Results for select head-to-head comparisons of interest (sulfonylurea, SGLT-2 and DPP-4 inhibitors, GLP-1 agonists, and insulins) are presented for each outcome where data were available.

Glycated haemoglobin (HbA1c)

Eighty-four RCTs reported mean change from baseline in HbA1c and were included in the reference case NMA.

Relative to metformin monotherapy, all of the selected classes significantly reduced mean difference in the change from baseline in HbA1c. When the classes were compared with each other, DPP-4 inhibitors did not reduce HbA1c as much as sulfonylureas, TZD or GLP-1 agonists (random effects model, Table A).

Table A.
Glycated haemoglobin (%) – mean difference (MD) in change from baseline for selected class comparisons

Treatment	*Reference*	*MD (95% CrI) from reference case*
MET+SUL	MET	**–0.70 (–0.83, –0.58)**
MET+DPP-4		**–0.58 (–0.68, –0.48)**
MET+SGLT-2		**–0.67 (–0.84, –0.49)**
MET+GLP-1		**–0.88 (–1.05, –0.71)**
MET+TZD		**–0.77 (–0.92, –0.63)**
MET+INS-BA		**–0.85 (–1.16, –0.53)**
MET+INS-BI		**–0.94 (–1.41, –0.48)**
MET+DPP-4	MET+SUL	**0.12 (0.01, 0.24)**
MET+SGLT-2		0.04 (–0.16, 0.24)
MET+GLP-1		–0.18 (–0.35, 0.00)
MET+TZD		–0.07 (–0.20, 0.07)
MET+INS-BA		–0.15 (–0.45, 0.17)
MET+INS-BI		–0.24 (–0.69, 0.21)
MET+SGLT-2	MET+DPP-4	–0.09 (–0.28, 0.10)
MET+GLP-1		**–0.30 (–0.46, –0.13)**
MET+TZD		**–0.19 (–0.33, –0.05)**
MET+INS-BA		–0.27 (–0.57, 0.04)
MET+INS-BI		–0.36 (–0.82, 0.10)
MET+GLP-1	MET+SGLT-2	–0.21 (–0.45, 0.03)
MET+TZD		–0.11 (–0.32, 0.11)
MET+INS-BA		–0.18 (–0.53, 0.18)
MET+INS-BI		–0.27 (–0.76, 0.22)
MET+TZD	MET+GLP-1	0.11 (–0.09, 0.30)
MET+INS-BA		0.03 (–0.27, 0.33)
MET+INS-BI		–0.06 (–0.53, 0.41)
MET+INS-BA	MET+TZD	–0.08 (–0.40, 0.25)
MET+INS-BI		–0.17 (–0.63, 0.30)
MET+INS-BI	MET+INS-BA	–0.09 (–0.56, 0.37)

Random-effect model	Residual deviance 166 vs 179 data points Deviance information criteria –170.795

MET = metformin, SUL = sulfonylurea, DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, INS-BA = basal insulin, INS-BI = biphasic insulin

Statistically significant differences are shown in bold

Body weight

Seventy RCTs reported changes from baseline body weight and were included in the reference case NMA.

Relative to metformin monotherapy, sulfonylurea, TZD and basal insulin combinations with metformin significantly increased mean body weight (range 2.1–2.8 kg) with no significant differences between these classes. SGLT-2 inhibitors and GLP-1 agonists added on to metformin were associated with significant reductions in mean body weight relative to metformin monotherapy (range –1.4 kg to –2.2 kg).

When the classes were compared, all non-insulin treatments added to metformin, except TZD, resulted in significant reductions in mean body weight relative to sulfonylurea (range –1. 9 kg to –4.3 kg). SGLT-2 inhibitors and GLP-1 agonists also resulted in significant reductions in mean body weight relative to DPP-4 inhibitors, while TZD and basal insulin resulted in significant increases in mean body weight from baseline. TZD, basal and biphasic insulin added to metformin significantly increased mean body weight from baseline relative to SGLT-2 inhibitors and GLP-1 agonists (Table B).

Table B.

Body weight (kg) – mean difference (MD) in change from baseline for selected class comparisons

Treatment	***Reference***	***MD (95% CrI) from reference case***
MET+SUL	MET	**2.11 (1.59, 2.63)**
MET+DPP-4		0.18 (–0.22, 0.58)
MET+SGLT-2		**–2.21 (–2.75, –1.67)**
MET+GLP-1		**–1.44 (–2.07, –0.81)**
MET+TZD		**3.20 (2.57, 3.82)**
MET+INS-BA		**2.76 (1.56, 4.01)**
MET+INS-BI		2.91 (0.85, 5.04)
MET+DPP-4	MET+SUL	**–1.93 (–2.37, –1.49)**
MET+SGLT-2		**–4.32 (–5.00, –3.66)**
MET+GLP-1		**–3.55 (–4.26, –2.85)**
MET+TZD		1.09 (0.48, 1.70)
MET+INS-BA		0.65 (–0.57, 1.95)
MET+INS-BI		0.80 (–1.26, 2.96)
MET+SGLT-2	MET+DPP-4	**–2.39 (–2.98, –1.80)**
MET+GLP-1		**–1.62 (–2.25, –0.99)**
MET+TZD		**3.02 (2.43, 3.61)**
MET+INS-BA		**2.59 (1.41, 3.82)**
MET+INS-BI		2.73 (0.70, 4.84)
MET+GLP-1	MET+SGLT-2	0.78 (–0.02, 1.57)
MET+TZD		**5.41 (4.63, 6.18)**
MET+INS-BA		**4.98 (3.68, 6.31)**
MET+INS-BI		**5.13 (3.03, 7.30)**

MET+TZD	MET+GLP-1	**4.64 (3.85, 5.42)**
MET+INS-BA		**4.20 (3.03, 5.40)**
MET+INS-BI		**4.35 (2.33, 6.46)**
MET+INS-BA	MET+TZD	–0.44 (–1.70, 0.90)
MET+INS-BI		–0.29 (–2.39, 1.90)
MET+INS-BI	MET+INS-BA	0.15 (–1.54, 1.82)

Random-effect model	Residual deviance 138.4 vs 148 data points Deviance information criteria 307.531

MET = metformin, SUL = sulfonylurea, DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, INS-BA = basal insulin, INS-BI = biphasic insulin.

Statistically significant differences are shown in bold

All-cause mortality, cardiovascular mortality and heart failure

Because of the low event rate and the large number of zero events in the data set, the NMA models for all-cause mortality, cardiovascular mortality and heart failure were not robust. Pairwise meta-analyses found no difference in the relative risks. The estimated confidence intervals were wide, again because of the paucity of events. No other direct estimates could be made.

Question 2. Patients at high risk for cardiovascular events

For question 2, 66 papers representing 17 unique RCTs were included in the systematic review. References are reported in the original application.

All but one of the studies were double-blind and all were funded by a pharmaceutical company. The sample size ranged from 304 to 16 492. The threshold baseline HbA1c level for inclusion in the trials was typically 6.5%, although some used a threshold as low as 6.0%. The mean baseline duration of diabetes ranged from 5.6 years to 13.4 years.

The included RCTs enrolled patients on various background therapies, and pragmatically allowed for continuation of whatever the existing background therapy was at baseline. In general, therefore, participants added the study intervention to their existing therapy. Background therapies were: no treatment (i.e. participants were drug-naïve when they started the study intervention); monotherapy (participants were taking a single antidiabetic medication or insulin and added the study intervention to that therapy); dual therapy; and combinations of more than two therapies. Monotherapy was predominantly metformin or insulin and dual therapy predominantly metformin plus a sulfonylurea or insulin.

Most studies enrolled participants at high risk of cardiovascular events or with cardiovascular disease. Mean body mass index (BMI) was between 25.2 (SD 3.0) and 32.5 (SD 6.3).

Most of the included RCTs were at overall low risk of bias. A total of 72% of RCTs were judged to be at low risk of bias for random sequence generation and allocation concealment. Since all the outcomes of interest were considered to be objective, all RCTs were judged to be at low risk of bias for outcome assessment. Most trials were judged to be at low risk of

bias (67%) for incomplete outcome data.

While carrying out the risk of bias assessments, reviewers noted that there were some limitations that should be noted in the cardiovascular RCTS, including the use of outcome definitions that may deviate from what would be considered standard (EMPA-REG OUTCOME), and lack of control for type 1 error (LEADER and EMPA-REG OUTCOME, exploratory analyses were not adjusted for). Other concerns included protocol amendments made after an interim analysis (EMPA-REG OUTCOME) and a number of participants cin the LEADER study who completed or discontinued the study before having an outcome after their last visit.

All-cause mortality

A total of 8 RCTs (*n* = 66 311) reported all-cause mortality and were included in the reference case analysis. Compared with placebo and DPP-4 inhibitors, SGLT-2 inhibitors – but none of the other treatments – reduced the risk of all-cause mortality (Table C).

Table C. *All-cause mortality – hazard ratios (HR) for all class comparisons*

Treatment	*Reference*	*HR (95% CrI)*
DPP-4	Placebo	1.02 (0.83, 1.20)
SGLT-2		**0.67 (0.47, 0.95)**
GLP-1		0.89 (0.71, 1.12)
TZD		0.91 (0.71, 1.16)
SGLT-2	DPP-4	**0.66 (0.45, 0.99)**
GLP-1		0.87 (0.67, 1.19)
TZD		0.90 (0.67, 1.24)
GLP-1	SGLT-2	1.32 (0.89, 2.03)
TZD		1.36 (0.90, 2.09)
TZD	GLP-1	1.03 (0.74, 1.42)

Random-effect model	Total residual deviance 7.678 vs 8 data points Deviance information criteria –10.022

DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, TZD = thiazolidinediones

Statistically significant differences are shown in bold.

Cardiovascular mortality

Six RCTs (*n* = 30 439) reported cardiovascular mortality and were included in the reference case analysis. Compared with placebo and with each other, none of the selected classes significantly lowered the risk of cardiovascular mortality (Table D).

Table D. *Cardiovascular mortality – hazard ratios (HR) for all class comparisons*

Treatment	*Reference*	*HR (95% CrI)*
DPP-4	Placebo	0.97 (0.33, 2.68)
SGLT-2		0.58 (0.14, 2.55)
GLP-1		0.86 (0.30, 2.47)
TZD		0.83 (0.20, 3.73)
SGLT-2	DPP-4	0.60 (0.10, 3.72)
GLP-1		0.89 (0.22, 4.03)
TZD		0.86 (0.15, 5.27)
GLP-1	SGLT-2	1.48 (0.25, 8.94)
TZD		1.42 (0.18, 11.65)
TZD	GLP-1	0.96 (0.15, 6.20)

Random-effect model	Total residual deviance 6.063 vs 6 data points Deviance information criteria –2.803

DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, TZD = thiazolidinediones

Summary of evidence – harms (from the application)

Question 1. Patients inadequately controlled on metformin

Severe hypoglycaemia

Severe hypoglycaemia was typically defined as an event requiring third-party assistance. Forty-eight RCTs reported severe hypoglycaemia and were included in the reference case NMA.

None of the classes significantly increased severe hypoglycaemia when compared with metformin monotherapy. When compared with each other, the GLP-1 agonists, SGLT-2 inhibitors and DPP-4 inhibitors significantly reduced the risk of severe hypoglycaemia relative to sulfonylureas (Table E).

Table E.

Severe hypoglycaemia – odds ratios (OR) for selected class comparisons

Treatment	*Reference*	*OR (95% CrI)*
MET+SUL	MET	**6.40 (2.24, 17.51)**
MET+DPP-4		0.91 (0.34, 2.41)
MET+SGLT-2		0.61 (0.13, 2.36)
MET+GLP-1		1.80 (0.63, 5.96)
MET+TZD		2.32 (0.30, 16.08)
MET+INS-BA		3.08 (0.65, 27.65)
MET+INS-BI		3.36 (0.33, 91.77)
MET+DPP-4	MET+SUL	**0.14 (0.07, 0.26)**
MET+SGLT-2		**0.09 (0.02, 0.44)**
MET+GLP-1		**0.29 (0.09, 0.89)**
MET+TZD		0.36 (0.04, 2.65)
MET+INS-BA		0.52 (0.10, 2.83)
MET+INS-BI		0.55 (0.06, 8.71)
MET+SGLT-2	MET+DPP-4	0.66 (0.15, 2.98)
MET+GLP-1		2.02 (0.68, 6.16)
MET+TZD		2.54 (0.32, 19.19)
MET+INS-BA		3.61 (0.74, 20.31)
MET+INS-BI		3.92 (0.42, 60.32)
MET+GLP-1	MET+SGLT-2	2.97 (0.61, 17.70)
MET+TZD		3.89 (0.33, 35.21)
MET+INS-BA		5.25 (0.73, 56.37)
MET+INS-BI		5.54 (0.44, 139.60)
MET+TZD	MET+GLP-1	1.20 (0.15, 10.72)
MET+INS-BA		1.73 (0.36, 12.74)
MET+INS-BI		1.91 (0.18, 34.90)
MET+INS-BA	MET+TZD	1.37 (0.15, 30.36)
MET+INS-BI		1.45 (0.09, 67.31)
MET+INS-BI	MET+INS-BA	1.04 (0.16, 11.39)

Random-effect model	Residual deviance 57.31 vs 100 data points Deviance information criteria 299.795

MET = metformin, SUL = sulfonylurea, DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, INS-BA = basal insulin,

INS-BI = biphasic insulin

Statistically significant differences are shown in bold.

Non-severe hypoglycaemia

The clinical definition of non-severe hypoglycaemia varied across the included RCTs. As in previous reviews, the most common differences were the specific blood glucose threshold for hypoglycaemia and whether patients were required to validate symptoms of hypoglycaemia with self-monitoring of blood glucose.

Sixty-seven RCTs reported at least one episode of non-severe hypoglycaemia and were included in the reference case NMA.

Compared with metformin monotherapy, the odds of non-severe hypoglycaemia were higher with sulfonylurea, basal and biphasic insulin. When the classes were compared, all except biphasic insulin significantly reduced odds of non-severe hypoglycaemia relative to sulfonylurea (Table F). Relative to DPP-4 and SGLT-2 inhibitors and GLP-1 agonists, basal and biphasic insulin significantly increased the odds of non-severe hypoglycaemia; moreover, biphasic insulin significantly increased the odds relative to basal insulin.

Table F.

Non-severe hypoglycaemia – odds ratios (OR) for selected class comparisons

Treatment	*Reference*	*OR (95% CrI) vs reference case*
MET+SUL	MET	**7.59 (5.25, 11.22)**
MET+DPP-4		0.77 (0.55, 1.10)
MET+SGLT-2		1.00 (0.62, 1.58)
MET+GLP-1		0.75 (0.46, 1.25)
MET+TZD		0.58 (0.32, 1.01)
MET+INS-BA		**3.18 (1.73, 5.80)**
MET+INS-BI		**6.92 (3.34, 14.52)**
MET+DPP-4	MET+SUL	**0.10 (0.07, 0.14)**
MET+SGLT-2		**0.13 (0.08, 0.21)**
MET+GLP-1		**0.10 (0.06, 0.16)**
MET+TZD		**0.08 (0.04, 0.14)**
MET+INS-BA		**0.42 (0.24, 0.72)**
MET+INS-BI		0.91 (0.46, 1.77)
MET+SGLT-2	MET+DPP-4	1.29 (0.79,2.07)
MET+GLP-1		0.97 (0.60, 1.56)
MET+TZD		0.74 (0.41, 1.35)
MET+INS-BA		**4.13 (2.35, 7.05)**
MET+INS-BI		**8.96 (4.47, 17.61)**
MET+GLP-1	MET+SGLT-2	0.75 (0.41, 1.41)
MET+TZD		0.58 (0.29, 1.16)
MET+INS-BA		**3.19 (1.63, 6.38)**
MET+INS-BI		**6.96 (3.17, 15.54)**
MET+TZD	MET+GLP-1	0.77 (0.37, 1.52)
MET+INS-BA		**4.25 (2.34, 7.52)**
MET+INS-BI		**9.25 (4.40, 19.24)**
MET+INS-BA	MET+TZD	**5.56 (2.55, 11.87)**
MET+INS-BI		12.13 (5.01, 28.48)
MET+INS-BI	MET+INS-BA	**2.18 (1.24, 3.85)**

Random-effect model	Residual deviance 128.8 vs 140 data points Deviance information criteria 678.986

MET = metformin, SUL = sulfonylurea, DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, INS-BA = basal insulin, INS-BI = biphasic insulin

Statistically significant differences are shown in bold.

Severe adverse events

Sixty-six RCTs reported serious adverse events and were included in the reference case NMA. Data were available for all drug classes. Compared with metformin monotherapy and with each other, none of the classes significantly increased or decreased the odds of serious adverse events (Table G).

Table G.

Serious adverse events – odds ratios (OR) for selected class comparisons

Treatment	*Reference*	*OR (95% CrI)*
MET+SUL	MET	0.96 (0.76, 1.21)
MET+DPP-4		0.91 (0.72, 1.15)
MET+SGLT-2		1.11 (0.83, 1.51)
MET+GLP-1		1.05 (0.71, 1.51)
MET+TZD		1.05 (0.81, 1.37)
MET+INS-BA		1.48 (0.63, 3.74)
MET+INS-BI		1.73 (0.42, 8.43)
MET+DPP-4	MET+SUL	0.95 (0.82, 1.10)
MET+SGLT-2		1.17(0.87, 1.55)
MET+GLP-1		1.10 (0.74, 1.61)
MET+TZD		1.09 (0.89, 1.37)
MET+INS-BA		1.54 (0.67, 3.83)
MET+INS-BI		1.83 (0.45, 8.70)
MET+SGLT-2	MET+DPP-4	1.23 (0.91, 1.66)
MET+GLP-1		1.16 (0.80, 1.66)
MET+TZD		1.15 (0.92, 1.47)
MET+INS-BA		1.63 (0.72, 4.02)
MET+INS-BI		1.93 (0.47, 9.13)
MET+GLP-1	MET+SGLT-2	0.94 (0.60, 1.49)
MET+TZD		0.93 (0.69, 1.33)
MET+INS-BA		1.33 (0.55, 3.34)
MET+INS-BI		1.57 (0.38, 7.77)
MET+TZD	MET+GLP-1	1.00 (0.67, 1.51)
MET+INS-BA		1.41 (0.61, 3.46)
MET+INS-BI		1.68 (0.39, 7.83)
MET+INS-BA	MET+TZD	1.41 (0.58, 3.48)
MET+INS-BI		1.67 (0.40, 7.99)
MET+INS-BI	MET+INS-BA	1.18 (0.37, 4.11)

Random-effect model	Residual deviance 129.3 vs 140 data points Deviance information criteria 701.988

MET = metformin, SUL = sulfonylurea, DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, INS-BA = basal insulin, INS-BI = biphasic insulin

Question 2. Patients at high risk for cardiovascular events

Severe hypoglycaemia

Eight RCTs reported severe hypoglycaemia (*n* = 66 133) and were included in the reference case NMA. The percentage of participants with a severe hypoglycaemic event ranged from 0.3% to 3.3%. Compared with placebo, there was a significantly lower risk of severe hypoglycaemia with GLP-1 agonists but a significantly increased risk with TZD. There was a significantly lower risk of severe hypoglycaemia with GLP-1 agonists relative to DPP-4 inhibitors. TZD significantly increased the risk of severe hypoglycaemic events relative to both DPP-4 inhibitors and GLP-1 agonists, but the risk was not significantly different from that with SGLT-2 inhibitors (Table H).

Table H.

Severe hypoglycaemia – odds ratios (OR) for all class comparisons

Treatment	*Reference*	*OR (95% CrI)*
DPP-4	Placebo	1.18 (0.91, 1.54)
SGLT-2		0.82 (0.45, 1.47)
GLP-1		**0.71 (0.49, 0.99)**
TZD		**2.05 (1.11, 3.98)**
SGLT-2	DPP-4	0.69 (0.36, 1.33)
GLP-1		**0.60 (0.38, 0.92)**
TZD		1.74 (0.89, 3.51)
GLP-1	SGLT-2	0.87 (0.43, 1.70)
TZD		**2.52 (1.07, 5.98)**
TZD	GLP-1	**2.89 (1.44, 6.24)**

Random-effect model	Residual deviance 13.86 vs 16 data points Deviance information criteria 114.457

DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, TZD = thiazolidinediones

Statistically significant differences are shown in bold.

Severe adverse events

Six RCTs reported severe adverse events (*n* = 31 219) and were included in the reference case NMA. The percentage of people with serious adverse events ranged between 18% and 50%. Compared with placebo and with each other, none of the selected classes significantly differed in the risk of severe adverse events (Table I).

Table I.

Severe adverse events – odds ratios for all class comparisons

Treatment	*Reference*	*OR (95% CrI)*
SUL	Placebo	0.81 (0.37, 1.77)
DPP-4		0.92 (0.58, 1.47)
SGLT-2		0.94 (0.58, 1.50)
GLP-1		0.95 (0.68, 1.33)
TZD		0.92 (0.57, 1.49)
DPP-4	SUL	1.13 (0.46, 2.83)
SGLT-2		1.15 (0.46, 2.85)
GLP-1		1.17 (0.50, 2.72)
TZD		1.13 (0.61, 2.11)
SGLT-2	DPP-4	1.02 (0.52, 1.97)
GLP-1		1.03 (0.58, 1.81)
TZD		0.99 (0.51, 1.94)
GLP-1	SGLT-2	1.02 (0.57, 1.83)
TZD		0.98 (0.50, 1.96)
TZD	GLP-1	0.96 (0.54, 1.73)

Random-effect model	Residual deviance 11.8 vs 12 data points Deviance information criteria 117.501

SUL = sulfonylurea, DPP-4 = dipeptidyl peptidase 4 inhibitor, SGLT-2 = sodium-glucose co-transporter 2 inhibitor, GLP-1 = glucagon-like peptide-1 agonist, TZD = thiazolidinediones

In synthesis, based on network meta-analyses, adjunctive second-line therapies were associated with possible reductions in glycaemic control when compared with metformin monotherapy, with few differences between any of the active treatments. Sulfonylurea and GLP-1 agonists reduced glycated haemoglobin when compared with DPP-4 inhibitors; GLP-1 agonists and sulfonylurea reduced weight when compared with metformin monotherapy, while insulin and sulfonylurea increased weight when compared with the other classes. GLP-1 agonists and insulins increased the number of adverse events and withdrawals. In high-risk patients, SGLT-2 inhibitors were possibly associated with a reduction in all-cause mortality when compared with placebo and with DPP-4 agonists and SGLT-2 inhibitors were not associated with severe hypoglycaemia events.

Sulfonylurea and insulins increased non-severe hypoglycaemia when compared with metformin monotherapy and other classes. However, basal insulin was associated with fewer non-severe hypoglycaemia events when compared with sulfonylurea.

Additional evidence (not in the application)

N/A

WHO guidelines

WHO guidelines on type 2 diabetes are being developed but had not been finalized at the time of the Expert Committee meeting.

Costs/Cost–effectiveness

The application did not provide information on costs of medicines or on their cost–effectiveness.

Availability

Good

Other considerations

N/A

Committee recommendations

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.

Supplementary tables

Second-line treatments for type 2 diabetes: oral medicines

Drug class	*International Nonproprietary Names*	*ATC codes*	*Dose form(s) and strength(s)*
Single-drug products			
DPP-4 inhibitors	alogliptin	A10BH04	Tablet: 6.25, 12.5, 25 mg
	linagliptin	A10BH05	Tablet: 5 mg
	saxagliptin	A10BH03	Tablet: 2.5, 5 mg
	sitagliptin	A10BH01	Tablet: 25, 50, 100 mg
SGLT-2 inhibitors	canagliflozin	A10BK02	Tablet: 100, 300 mg
	dapagliflozin	A10BK01	Tablet: 5, 10 mg
	empagliflozin	A10BK03	Tablet: 10, 25 mg
Sulfonylureas	chlorpropamide	A10BB02	Tablet: 100, 250 mg
	gliclazide	A10BB02	Tablet: 40, 80 mg
	glimepiride	A10BB12	Tablet: 1, 2, 3, 4 mg
	glibenclamide/ glyburide	A10BB04	Tablet: 2,5 mg, 5
	tolbutamide	A10BB03	Tablet: 500 mg
TZDs	pioglitazone	A10BG03	Tablet: 15, 30, 45 mg
	rosiglitazone	A10BG02	Tablet: 4 mg, 8
Meglitinides	nateglinide	A10BX03	Tablet: 60, 120, 180 mg
	repaglinide	A10BX02	Tablet: 500 µg, 1 mg, 2 mg
AGIs	acarbose	A10BF01	Tablet: 50, 100 mg
Fixed-dose combination drug products			
DPP-4 inhibitors + biguanides	alogliptin + metformin	A10BD13	Tablet: 12.5 + 500 mg 12.5 + 850 mg 12.5 + 1000 mg
	linagliptin + metformin	A10BD19	Tablet: 2.5 + 500 mg 2.5 + 850 mg 2.5 + 1000 mg
	saxagliptin + metformin	A10BD21	Tablet: 2.5 + 1000 mg 5 + 500 mg 5 + 1000 mg
	sitagliptin + metformin	A10BD07	Tablet: 50 + 500 mg 50 + 850 mg 50 + 1000 mg 100 + 1000 mg

SGLT-2 inhibitors + biguanides	dapagliflozin + metformin	A10BD15	Tablet: 5 + 850 mg 5 + 1000 mg
	empagliflozin + metformin	A10BD20	Tablet: 12.5 + 850 mg 5 + 850 mg 12.5 + 1000 mg 5 + 1000 mg
	canagliflozin + metformin	A10BD16	Tablet: 50 + 850 mg 50 +1000 mg

Second-line treatments for type 2 diabetes: injectable medicines and insulin analogues

Drug class and International Nonproprietary Names		***ATC codes***	***Dose form(s) and strength(s)***
GLP-1 agonist products			
dulaglutide		A10BJ05	Injection: 1.5 mg/1 mL, 3 mg/1mL
exenatide		A10BJ01	Injection: 250 µg/1 mL
exenatide extended-release		A10BJ01	Powder: 2 mg
liraglutide		A10BJ02	Injection: 6 µg/1 mL
albiglutide		A10BJ04	Powder: 30 mg, 50 mg
Insulin and insulin analogues			
Insulin and insulin analogue products	*Insulin and insulin analogue types*		
insulin aspart	Very rapid-acting insulin analogue	A10AB05	100 units/1 mL
insulin glulisine	Very rapid-acting insulin analogue	A10AB06	100 units/1 mL 200 units/1 mL
insulin lispro	Very rapid-acting insulin analogue	A10AB04	100 units/1 mL 200 units/1 mL
insulin, regular	Rapid-acting insulin	A10AB01	100 units/1 mL
insulin, pork	Rapid-acting insulin	A10AB03	100 units/1 mL
insulin, NPH	Intermediate-acting insulin	A10AC01	100 units/1 mL
insulin, pork	Intermediate-acting insulin	A10AC03	100 units/1 mL
insulin detemir	Long-acting insulin analogue	A10AE05	100 units/1 mL
insulin glargine	Long-acting insulin analogue	A10AE04	100 units/1 mL 300 units/mL
insulin regular/ insulin, NPH	Mixed (regular/NPH) human insulin	A10AD01	30 units/mL + 70 units/mL
insulin lispro/ lispro protamine	Mixed insulin analogue	A10AD04	25 units/mL + 75 units/ mL 50 units/mL + 50 units/mL

insulin aspart/aspart protamine	Mixed insulin analogue	A10AD05	30 units/mL + 70 units/mL

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Section 21: Ophthalmological preparations

21.1: Anti-infective agents

Natamycin – addition – EML and EMLc

Natamycin **ATC Code: S10AA10**

Proposal

The application requested addition of natamycin ophthalmic suspension to the core list of the EML and EMLc for the treatment of corneal fungal keratitis.

Applicant(s)

Global Action Fund for Fungal Infection, Geneva, Switzerland, in association with the International Centre for Eye Health, Faculty of Infectious & Tropical Diseases, London School of Hygiene and Tropical Medicine, London, England, and Manchester University, Manchester, England

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WHO technical department

N/A

EML/EMLc

EML and EMLc

Section

Section 21.1 Anti-infective agents

Dose form(s) and strength(s)

Suspension (eye drops): 5%

Core/Complementary

Core

Individual/Square box listing

Individual

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

Natamycin eye drops have not previously been considered for inclusion on the EML. Currently, no topical antifungals for ophthalmic infections are listed.

Public health relevance (burden of disease)

Keratitis refers to inflammation of the cornea, which causes ulceration and gradual opacification, initially due to an influx of inflammatory cells and later to fibrosis. Microbial keratitis may be caused by bacteria, fungi, viruses or protozoa (inflammation without infection may be due to chemical injury or autoimmune inflammatory pathology) and is the leading cause of unilateral corneal scarring (*1, 2*). Corneal abrasions or significant trauma from plant or organic material are the most common predisposing factors (*3*). Other risk factors include being immunocompromised (including exposure to local or systemic corticosteroids), diabetes, HIV infection, impaired tearing, incomplete eyelid closure and poor hygiene practice in those who use contact lenses. Children are often affected (*4*).

In warm, humid climates, approximately 50% of cases of microbial keratitis are caused by fungi, but in dry, cool climates, 95% of cases are caused by bacteria (*5*). The proportion of microbial keratitis cases attributable to fungal infections rises with proximity to the Equator (*6*).

An estimated 12 million cases of microbial keratitis occur annually in south-east Asia; the proportion of cases with resultant visual loss or blindness is unknown. A statistically significant correlation has been found between gross national income (GNI) and etiology of microbial keratitis: fungal keratitis is associated with low-GNI countries (*7*). In Ugandan children with visual impairment, visual loss after corneal ulceration was responsible for nearly 25% of cases (*8*). The rate of HIV infection in those presenting with fungal keratitis in United Republic of Tanzania was twice the documented rate in the adult population (*9*).

The annual incidence of microbial keratitis in wearers of contact lenses varies from 1.2 to 1304 per 10 000, depending on the type of lens, overnight use and the quality of lens care (*10, 11*). The proportion of microbial keratitis cases caused by fungi in contact lens wearers varies from 0.33% to 50% (*7*).

Summary of evidence – benefits (from the application)

The application summarized the findings of seven randomized controlled trials (RCTs) of natamycin compared with alternative treatments for fungal keratitis (*12–18*).

Two trials compared natamycin with chlorhexidine gluconate and found more favourable responses at 5 days, and a greater proportion of patients with healed ulcer at 21 days, for the chlorhexidine-treated groups than the natamycin-treated groups (*16, 17*). These trials had small sample sizes (n = 60 and n=71) and were therefore probably underpowered for detection of differences.

A single study comparing natamycin with econazole found no difference between the two treatments for the outcome measure of healed or healing ulcer at the final visit (risk ratio 0.99; 95% confidence interval 0.8–1.21) (*15*).

Three trials compared topical natamycin 5% with topical voriconazole 1% and measured best corrected spectacle visual acuity (BCSVA) at 3 months as the primary outcome (*12–14*). A meta-analysis of these trials in a recent Cochrane review suggested that: “there is evidence that natamycin is more effective than voriconazole in the treatment of fungal ulcers” (*19*). The largest of the three studies, referred to as MUTT1, found a substantial benefit for natamycin compared with voriconazole, particularly for *Fusarium* spp., which

are often the major cause (*14*).

Summary of evidence – harms (from the application)

The adverse events that have been identified during post-marketing use of natamycin in clinical practice are allergic reaction, change in vision, chest pain, corneal opacity, dyspnoea, eye discomfort, eye oedema, eye hyperaemia, eye irritation, eye pain, foreign body sensation, paraesthesia, and tearing. Clinical trial experience suggests that these events are rare and that topical natamycin is generally well tolerated (*14*).

Additional evidence (not in the application)

Six of the seven RCTs identified in the application were included in a recent systematic review and meta-analysis of natamycin for the treatment of fungal keratitis (20). The included trials were all conducted in Asian countries (Bangladesh, China, India) where there is a higher prevalence of fungal keratitis. The authors concluded that natamycin is a preferable treatment choice, particularly in the early stages of *Fusarium* cases.

WHO guidelines

The 2004 *Guidelines for the management of corneal ulcer at primary, secondary and tertiary care facilities in the South-East Asia region* "WHO regional Office for South-East Asia) recommend natamycin 5% eye drops for treatment of confirmed suppurative keratitis where fungal hyphae are seen on corneal smear (*1*).

Costs/Cost–effectiveness

The Expert Committee noted the considerable variation in the reported cost of topical natamycin 5% by region as described in the application: Indonesia US$ 4, Peru US$ 140, and United Kingdom £330 per bottle.

Availability

Topical natamycin has been used extensively for the treatment of fungal keratitis in south Asia and south-east Asia and North America and has recently become the standard of care in the United Kingdom. It is less widely used in Africa and continental Europe where it is not readily available.

Other considerations

N/A

Committee recommendations

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.

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

Bevacizumab – no change – EML

Bevacizumab **ATC Code: L01XC07**

Proposal

The application requested the deletion of bevacizumab for ophthalmic use from the EML *or* amendment to the current listing for bevacizumab to indicate that the product was not developed or approved by regulatory authorities for ocular use and that potential harm may be caused to patients by inappropriate handling and storage.

Applicant(s)

F. Hoffman-La Roche Ltd

WHO technical department

N/A

EML/EMLc

EML

Section

21.6 Anti-vascular endothelial growth factor (VEGF) preparations

Dose form(s) and strength(s)

Injection: 25 mg/mL

Core/Complementary

Complementary

Individual/Square box listing

Individual

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

Bevacizumab was added to the EML in 2013 for intravitreal administration for the treatment of neovascular age-related macular degeneration (nAMD). In making its recommendation, the 2013 Expert Committee concluded that, on the basis of the CATT (*1, 2*) and IVAN (*3*) comparative trials of bevacizumab and ranibizumab and the observational safety data, intraocular bevacizumab was effective and safe for the treatment of nAMD. The Committee noted that bevacizumab does not have regulatory approval for use in nAMD and highlighted the need for its safe preparation and intravitreal administration (*4*).

Bevacizumab was considered again by the Expert Committee in 2015 as part of its consideration of an application requesting the addition of ranibizumab to the EML for same indication. The Committee noted that there was substantial evidence from well-conducted independent studies showing bevacizumab and ranibizumab to be similarly effective and safe. Again, the Expert Committee acknowledged that bevacizumab is not specifically formulated for intravitreal administration and noted reports of adverse events, including endophthalmitis, resulting from administration of compounded bevacizumab. The Committee considered that the safe use of bevacizumab (as currently formulated) may require use to be restricted to a single patient per vial, or any alternative approach to comply with safe and sterile injection practices, and appropriate storage conditions, to prevent any possibility of contamination (*5*).

Public health relevance (burden of disease)

N/A

Summary of evidence – benefits (from the application)

N/A

Summary of evidence – harms (from application)

The application stated that sterility could be compromised during the process of compounding bevacizumab for intravitreal administration from its preservative-free, single-use vial, when multiple intravitreal doses are prepared from the same single-use vial.

The application described recent cases from Egypt, India and the Islamic Republic of Iran, in which some patients experienced adverse ocular events after intravitreal administration of bevacizumab.

The same cases were described, and a similar request was made to add clarifying language to the EML listing of bevacizumab, in correspondence from Roche to the Director-General of WHO, Dr Margaret Chan, in 2016.

The application referenced United States Pharmacopoeia standards for the manufacturing of IV drug formulations and ophthalmic solutions. The Pharmacopoeia states that the manufacturing requirements for IV drug formulations allow higher sub-visible particle counts than those for ophthalmic solutions and that bevacizumab is therefore not manufactured in accordance with the more stringent requirements for particulate matter in ophthalmic solutions.

Additional evidence (not in the application)

N/A

WHO guidelines

N/A

Costs/Cost–effectiveness

N/A

Availability

N/A

Other considerations

The Expert Committee acknowledged the potential risk of infection associated with non-sterile compounding and intravitreal injection of bevacizumab from single-use vials, and recalled the findings of the Expert Committee in both 2013 and 2015 of the need for safe and sterile compounding and administration techniques for intravitreal bevacizumab.

Committee recommendations

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.

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Section 22: Oxytocics and antioxytocics

22.1: Oxytocics

Misoprostol - no change - EML

Misoprostol **ATC Code: G02AD06**

Proposal

The application requested deletion of the listed indication of prevention of postpartum haemorrhage associated with misoprostol on the EML.

Applicant(s)

Dr Petra Sevcikova, Professor Allyson Pollock

WHO technical department

The Maternal and Perinatal Health, Preventing Unsafe Abortion unit of the WHO Department of Reproductive Health and Research (RHR) advised that the evidence presented in the application would be considered at a scoping meeting for updating the postpartum haemorrhage (PPH) guidelines at the end of March 2017. In the meantime, the RHR department did not support any changes to the listing of misoprostol on the EML.

EML/EMLc

EML

Section

22.1 Oxytocics

Dose form(s) and strength(s)

Tablet: 200 µg

Core/Complementary

Core

Individual/Square box listing

Individual

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

Misoprostol was added to the EML in 2011 for prevention of PPH in settings where parenteral uterotonics are not available or feasible. It was, and remains, listed with a conditional note specifying that its use in PPH is limited to circumstances where oxytocin is not available or cannot be safely used.

This is the third application from Dr Sevcikova and Professor Pollock requesting deletion of misoprostol for the prevention of PPH from the EML. Similar requests were considered by the Expert Committee in 2013 and 2015. The 2013 request was based on a reinterpretation of previously presented data, and the Expert Committee did not consider that it represented a basis for changing its previous decision to list. Similarly, in 2015, no new trials were presented that compared misoprostol and oxytocin for prevention of PPH; the Expert Committee saw no reason to draw different conclusions from those reached by the 2013 Expert Committee (listed below) and decided that the EML listing for misoprostol for prevention of PPH should remain.

- Misoprostol is less effective than oxytocin infusion and is associated with adverse events (vomiting and shivering).
- Misoprostol is an alternative for prevention of PPH in resource-poor, community and rural settings where IV oxytocin is unavailable or cannot be safely administered.

Public health relevance (burden of disease)

Postpartum haemorrhage has been identified as accounting for more than a quarter of maternal deaths and is the leading direct cause of maternal death globally (*1*). In 2015, the global maternal mortality was estimated to be 216 per 100 000 live births; reducing maternal mortality to fewer than 70 per 100 000 live births by 2030 is one of the United Nations Sustainable Development Goals (SDG 3.1) (*2*).

Summary of evidence – benefits (from the application)

The current application included an updated search for randomized controlled trials (RCTs) assessing misoprostol use in community and home birth settings in low- and middle-income countries. The updated search identified two new studies: a cluster randomized trial in a community setting in Senegal (*3*) and a systematic review and meta-analysis of RCTs comparing misoprostol with ergometrine–oxytocin for prevention of PPH (*4*).

Haemoglobin concentrations were recorded pre- and post-delivery in 1049 women given 10 IU oxytocin IM or 600 µg misoprostol orally at maternity huts in Senegal (*3*). No significant difference in haemoglobin decrease between treatment arms was observed (mean difference 0.3 g/L; 95% confidence interval (CI) –8.26 to 8.92; $P = 0.71$). The authors concluded that both drugs were safe and efficacious when delivered by auxiliary midwives. They also acknowledged the programmatic limitations of oxytocin, such as cold chain storage requirements, and considered that misoprostol could have advantages over oxytocin at the community level for prevention of PPH.

The application did not report the findings of the systematic review (*4*).

Summary of evidence – harms (from the application)

Both misoprostol and oxytocin were well tolerated in the trial in Senegal. Shivering was more common among misoprostol-treated patients and nausea more common among those given oxytocin. Eighteen stillbirths were reported in the study population, 6 in the misoprostol group and 12 in the oxytocin group.

Additional evidence (not in the application)

The current application identified a systematic review and meta-analysis in the updated literature search (*4*) but did not discuss the its findings. The review covered six RCTs that included 4034 women and compared the effects of misoprostol versus ergometrine–oxytocin in the prevention of PPH. Compared to ergometrine–oxytocin, misoprostol was associated with a statistically significantly higher rate of both PPH (7.6% vs 4.2%; relative risk (RR) 1.81; 95% CI: 1.40–2.35) and need for additional uterotonic therapy (19.2% vs 10.5%; RR 1.83; 95% CI 1.57–2.14). There was no difference in the rate of severe PPH between treatment groups (1.2% vs 0.76%; RR 1.55; 95% CI 0.78–3.07). The authors concluded that misoprostol could be used for prevention of PPH in situations where appropriate equipment and skilled attendants are not available. Ergometrine–oxytocin was considered an alternative treatment choice in low-resource settings.

The evidence that informed the 2012 *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (*5*) was based on a systematic review of seven trials directly comparing oxytocin and misoprostol and involving more than 22 000 women. Studies were conducted in hospital settings with interventions delivered by skilled attendants (*6*).

There was no difference in the rate of maternal deaths between treatment arms. Misoprostol 600 µg was associated with an increased risk of blood loss greater than 1000 mL compared with oxytocin 10 IU (RR 1.36; 95% CI 1.17–1.58). There was no statistically significant difference between treatment arms with regard to use of blood transfusions (RR 0.77; 95% CI 0.59–1.02). Use of additional uterotonics was greater with misoprostol compared with oxytocin (RR 1.4; 95% CI 1.31–1.5).

Compared with oxytocin, misoprostol was associated with higher rates of shivering (RR 3.3; 95% CI 3.0–3.5), diarrhoea (RR 2.52; 95% CI 1.6–3.98) and pyrexia (RR 6.8; 95% CI 5.5–8.3).

WHO guidelines

The 2012 *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (*5*) include the following recommendations for uterotonics in the prevention of PPH:

- The use of uterotonics for the prevention of PPH during the third stage of labour is recommended for all births (strong recommendation, moderate-quality evidence).
- Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH (strong recommendation, moderate-quality evidence).
- In settings where oxytocin is unavailable, the use of other injectable uterotonics

(if appropriate ergometrine/methylergometrine or the fixed-drug combination of oxytocin and ergometrine) or oral misoprostol (600 µg) is recommended (strong recommendation, moderate-quality evidence).

- In settings where skilled birth attendants are not present and oxytocin is unavailable, the administration of misoprostol (600 µg PO) by community health-care workers and lay health workers is recommended for the prevention of PPH (strong recommendation, moderate-quality evidence).
- Oxytocin (IV or IM) is the recommended uterotonic drug for the prevention of PPH in caesarean section (strong recommendation, moderate-quality evidence).

Costs/Cost–effectiveness

N/A

Availability

N/A

Other considerations

N/A

Committee recommendations

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.

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Section 25: Medicines acting on the respiratory tract

25.1: Antiasthmatics and medicines for chronic obstructive pulmonary disease

Budesonide + formoterol – addition - EML; rejection - EMLc

Budesonide + formoterol **ATC Code: R03AK07**

Proposal

The application requested addition of budesonide + formoterol combination inhaler to the core list of EML and EMLc as single-inhaler therapy for the management of asthma, in which a single inhaler can be used both as regular therapy to control the disease and as rescue therapy to relieve acute asthma symptoms – "maintenance and reliever therapy". Listing was requested with a square box symbol, representing alternative combination formulations containing an inhaled corticosteroid and a beta-2 agonist bronchodilator.

Applicant(s)

Professor Jean-William Fitting, Vice-Chair, Adult & Child Lung Health Section, International Union against Tuberculosis and Lung Disease, Paris, France

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WHO technical department

WHO Department of Noncommunicable Diseases, Disability, Violence and Injury Prevention

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EML/EMLc

EML and EMLc

Section

25.1 Antiasthmatics and medicines for chronic obstructive pulmonary disease

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Dose form(s) and strength(s)

EML (adults and adolescents ≥12 years):

dry powder inhaler: 100 µg +6 µg per dose; 200 µg + 6 µg per dose

EMLc (children 6–11 years):

dry powder inhaler: 100 µg +6 µg per dose

Core/Complementary

Core

Individual/Square box listing

Square box listing to represent alternative combination formulations containing an

inhaled corticosteroid (ICS) and a beta-2 agonist.

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

Single-ingredient inhalers containing budesonide are currently included on the EML and EMLc. The EML also includes the ICS beclometasone as a single-ingredient inhaler.

Salbutamol, a short-acting beta-2 agonist (SABA), is the only beta-2 agonist currently listed on the EML and EMLc. Formoterol is a long-acting beta-2 agonist (LABA). Both salbutamol and formoterol are full (as opposed to partial) beta-2 agonists, with the rapid onset of action essential for rescue/reliever therapy of acute asthmatic episodes (*1*).

Public health relevance (burden of disease)

The Global Asthma Network's *Global asthma report 2014* estimates that asthma affects approximately 334 million people globally and is the 14th most important disorder in terms of global years lived with disability. Although effective therapy exists for treating asthma, it is not currently available to most individuals with asthma living in low-income countries (*2*).

Summary of evidence – benefits (from the application)

The application presented the results of two systematic reviews of the comparative effectiveness of single-inhaler therapy with budesonide + formoterol as maintenance and reliever therapy versus current best practice (*3*) and versus combination inhaler maintenance therapy (*4*).

The combination of budesonide + formoterol as single-inhaler therapy was assessed against treatment of a control group with inhaled steroids and a separate reliever inhaler in 13 trials involving 13 152 adults; one of these trials also involved 224 children under 12 years of age (*3*).

Among adults not well controlled on ICS, there was no significant advantage for single-inhaler therapy over current best practice in terms of a reduction in exacerbations needing hospital admission (odds ratio (OR) 0.81; 95% confidence interval (CI) 0.45–1.44; low-quality evidence due to risk of bias and imprecision). Single-inhaler therapy significantly reduced the risk of exacerbations requiring treatment with oral corticosteroids (OR 0.83; 95% CI 0.70–0.98; moderate-quality evidence due to risk of bias). Most trials found a reduction of total ICS dose when single-inhaler therapy was used.

The study that included children compared single-inhaler therapy with higher-dose budesonide. Among patients using single inhaler therapy, there was a significant reduction in the number experiencing exacerbations that required increased ICS or other treatment (OR 0.33; 95% CI 0.1– 0.77).

Single-inhaler therapy with budesonide + formoterol as maintenance and reliever therapy was compared with higher-dose ICS/LABA combination inhaler maintenance therapy plus SABA reliever in four studies involving 9130 adolescent and adult patients with asthma (*4*). The number of people who had at least one severe exacerbation requiring hospitalization or an emergency outpatient visit was significantly lower in the single-inhaler therapy group (OR 0.72; 95% CI 0.57–0.90; high-quality evidence)). The number of people who

had an exacerbation requiring a course of oral steroids was also significantly lower in the single-inhaler therapy group (OR 0.75; 95% CI 0.65–0.87; high-quality evidence). Nocturnal awakenings were significantly reduced in the single-inhaler therapy group.

Summary of evidence – harms (from the application)

Evidence for the safety of budesonide was evaluated at the time of listing and was not discussed further.

Formoterol shares the known side-effects of beta-2 adrenergic receptor agonists, including increased heart rate and palpitations, transient decrease in arterial partial pressure of oxygen (PaO2) in patients with airway obstruction, increased glycogenolysis and hyperglycaemia, hypokalaemia, and dose-related tremor (*5*).

The application presented the results of a systematic review of 20 trials involving 10 578 adolescents and adults and seven studies of 2788 children and adolescents to assess the risk of fatal and non-fatal serious adverse events in individuals with chronic asthma given regular formoterol with ICS over 12 weeks versus the same dose of ICS alone (*6*).

Among adults, six deaths occurred in the ICS + formoterol group versus one in the ICS alone group; the difference was not statistically significant (OR 3.56; 95% CI 0.79–16.03, low-quality evidence). In adults and adolescents, there was no difference in the proportions of non-fatal serious adverse events between treatment groups (OR 0.98; 95% CI 0.76–1.27; moderate-quality evidence). Among children, there was weak, moderate-quality evidence of an increase in non-fatal serious adverse events in the formoterol + ICS group (OR 1.62; 95% CI 0.80–3.28). Asthma-related serious events were lower in the formoterol + ICS arm among adults (OR 0.49; 95% CI 0.28–0.88, moderate-quality evidence), but a greater number were reported in children. However, this finding was not statistically significant (OR 1.49; 95% CI 0.48–4.61; low-quality evidence).

Both systematic reviews found there to be no significant differences in fatal or non-fatal serious adverse events between treatment groups (*3, 4*).

Additional evidence (not in the application)

N/A

WHO guidelines

There are no current WHO guidelines for the treatment of asthma.

Recommendations of the Global Initiative for Asthma (GINA) in *Global strategy for asthma management and prevention* are for low-dose ICS + formoterol as both maintenance and reliever therapy for moderate and severe asthma in adults and adolescents (*7*).

The *British guidelines on the management of asthma* state that it is generally considered that combination ICS + LABA inhalers will aid adherence and have the advantage of ensuring LABA is not administered without ICS. The guidelines also state that efficacy studies have revealed no difference in efficacy between giving ICS and LABA in combination and giving them separately in circumstances where there is good adherence. The guidelines recommend that patients taking budesonide + formoterol as rescue/reliever therapy at

least daily on a regular basis should be reviewed (*8*).

Costs/Cost–effectiveness

The application estimates the annual treatment costs for low-dose budesonide + formoterol in the United Kingdom to be £181–230 and of high-dose budesonide + formoterol to be £363–461.

Two studies assessed the cost–effectiveness of budesonide + formoterol versus ICS alone (*9, 10*). In both studies patients receiving budesonide + formoterol therapy had more symptom-free days and fewer exacerbation events than patients given budesonide or fluticasone alone. In one study, the budesonide + formoterol therapy cost slightly more than ICS alone. The incremental cost–effectiveness ratio (ICER) was €2.32 (US$ 2.62) per symptom-free day gained (*9*). In the second study, the budesonide + formoterol therapy was dominant (more effective, and less expensive at €80 or US$ 90 less per patient over 12 weeks) (*10*).

Cost–effectiveness of the single-inhaler therapy was also assessed in other several studies versus a higher-dose ICS plus SABA reliever therapy, or a similar ICS/LABA therapy plus SABA or LABA reliever therapy, or a higher-dose ICS/LABA therapy plus SABA reliever therapy. In most comparisons, the budesonide + formoterol single-inhaler therapy was more effective at lower total cost and was thus dominant (*11*).

Availability

Budesonide + formoterol is available as Symbicort Turbuhaler® (AstraZeneca) and DuoResp Spiromax® (TEVA Pharma B.V)

Other considerations

Current British guidelines recommend the single-inhaler therapy at steps 2–3 of treatment and higher but do not address the question of asthma management in resource-limited settings. The role of single-inhaler therapy should be investigated for all levels of asthma severity in resource-limited settings (*12*).

Committee recommendations

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.

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

26.3: Miscellaneous

Ready to use therapeutic food (RUTF) – rejection – EMLc

Ready-to-use therapeutic food (RUTF) **ATC code: n/a**

Proposal

The application proposed the addition of ready-to-use therapeutic food (RUTF) to the core list of the EMLc for the dietary management of uncomplicated severe acute malnutrition (SAM) in children from 6 to 59 months of age.

Applicant(s)

Action Contre la Faim (ACF), France

WHO technical department

Evidence and Programme Guidance unit, Department of Nutrition for Health and Development

EML/EMLc

EMLc

Section

26.3 Miscellaneous

Dose form(s) and strength(s)

Lipid-based paste for oral consumption

Nutritional composition per 100 g:	
Energy	520–550 kcalth
Proteins	10–12% total energy (12.8–16.2% by weight)
Lipids	45–60% total energy (25.8–36.3% by weight)
N-6 fatty acids	3–10% total energy
N-3 fatty acids	0.3–2.5% total energy
Trans-fatty acids	<3% of total fat
Fibre	<5%
Vitamin A (retinol equivalent)	0.8–1.2 mg
Vitamin D (colecalciferol)	15–20 µg
Vitamin C (ascorbic acid)	50 mg minimum
Vitamin E (tocopherol)	20 mg minimum
Vitamin K (phytomenadione)	15–30 µg
Vitamin B1 (thiamine)	0.5 mg minimum
Vitamin B2 (riboflavin)	1.6 mg minimum
Vitamin B6 (pyridoxine)	0.6 mg minimum
Vitamin B12 (cyanocobalamin)	1.6 µg minimum
Vitamin B9 (folic acid)	200 µg minimum
Vitamin B3 (niacin)	5 mg minimum
Vitamin B5 (pantothenic acid)	3 mg minimum
Vitamin B7 (biotin)	60 µg minimum
Sodium	290 mg maximum
Potassium	1100–1400 mg
Calcium	300–600 mg
Phosphorus	300–600 mg
Magnesium	80–140 mg
Iron	10–14 mg
Zinc	11–14 mg
Copper	1.4–1.8 mg
Selenium	20–40 µg
Iodine	70–140 µg

1 $kcal_{th}$ = 4.184 kJ

Core/Complementary

Core

Individual/Square box listing

Individual

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

Therapeutic foods have not been previously considered for inclusion on the EML or EMLc. The EML and EMLc do not currently include any therapeutic foods.

Public health relevance (burden of disease)

Severe acute malnutrition is a significant cause of child mortality worldwide. It is estimated that more than 17 million children are affected by SAM globally, with less than 20% of affected children accessing treatment in 2013 (*1*).

Annually, around 35% of deaths among children under 5 years of age are due to nutrition-related factors, with almost 5% attributable to severe wasting (*2*).

Summary of evidence – benefits (from the application)

The application presented the results of two systematic reviews and one clinical trial for the treatment of SAM in children aged 6-59 months.

A 2013 Cochrane systematic review and meta-analysis of three quasi-randomized trials involving children aged 6 months to 5 years with SAM that compared RUTF with a standard flour porridge found that RUTF improved recovery slightly (risk ratio (RR) 1.32; 95% confidence interval (CI) 1.16–1.50). The evidence was considered to be of low quality, downgraded for risk of bias and indirectness. The evidence for relapse, mortality and weight gain was graded as very low quality and was too limited to enable definitive conclusions to be drawn for these outcomes (*3*).

A systematic review and meta-analysis of treatment of severe and moderate acute malnutrition compared children who received RUTF with those who received standard care (inpatient treatment followed by provision of corn soy blend (CSB) food for feeding at home). The evidence was also graded as low quality and limited (the review included largely the same studies as the Cochrane Review). Children given RUTF for community-based treatment of SAM were found to be 51% more likely to achieve nutritional recovery than the standard care group (RR 1.51; 95% CI 1.04–2.20). Weight gain in the RUTF group was also statistically significantly higher, albeit small (mean difference (MD) 1.27; 95% CI 0.16–2.38). There were no significant differences in mortality between the two groups (*4*). Because of the lack of high-quality comparative trials evaluating community-based treatment using RUTF, the authors complemented their systematic review and meta-analysis with a Delphi process to gather and synthesize expert opinion on the plausible impact estimates of the intervention. For community-based treatment of uncomplicated SAM using RUTF, the Delphi process estimated the case-fatality rate at 4% (range 2¬–7%) and the recovery rate at 80% (range: 50–93%). Overall, the review argued that the

community-based management of uncomplicated SAM in children aged 6–59 months is backed by a wealth of observational and programmatic data despite the limited number of impact studies (*4*).

Results of an additional cluster-randomized clinical trial in India of 26 children with uncomplicated SAM were presented. The study found that children who received RUTF in addition to standard supplementary nutrition (500 kcal of energy and 12–15 g protein) were 10 times more likely to recover (odds ratio (OR) 10.28; 95% CI 1.02–104.95) (5).

Summary of evidence – harms (from the application)

For peanut-based RUTFs, the largest safety concern is aflatoxin. The maximum aflatoxin level that is safe for consumption has been reported as 5 parts per billion (ppb) (*6*). In 2013–2014, 99.5% of RUTF tested by the Supply Division of the United Nations Children's Fund (UNICEF) contained less than 5 ppb aflatoxin.

No difference in mortality was found between children who received RUTF and those who received standard diets (RR 0.97; 95% CI 0.46–2.05; *n* = 599) and no difference in the frequency of diarrhoea between treatment groups (MD –0.6; 95% CI –1.30 to 0.10; *n* = 352) (*3*).

Additional evidence (not in the application)

The FAO/WHO joint commission of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) is currently developing guidelines for RUTF.

WHO guidelines

The proposed formulation and nutritional composition are consistent with the nutritional composition of RUTF recommended in in the joint WHO, World Food Programme, United Nations System Standing Committee on Nutrition and UNICEF statement on community-based management of severe acute malnutrition (*6*).

Therapeutic feeding approaches involving RUTF in the management of SAM in children aged 6–59 months are recommended in WHO's *Guideline: updates on the management of severe acute malnutrition in infants and children* (*7*).

Costs/Cost–effectiveness

While total cost of treatment can vary significantly, the absolute cost of RUTF product procurement and transportation is more consistent across programmes. In the published literature, the cost of RUTF per child treated ranged from US$ 39.6 to US$ 104.65 (*8–13*).

In addition to cost–effectiveness per child treated, a small number of studies also included analysis of cost per disability-adjusted life-year (DALY) or life saved. Studies in Malawi and Zambia estimated cost–effectiveness to be US$ 42–53 per DALY or US$ 1365–1760 per life saved (*9, 10*). A recent cost–effectiveness analysis of a large-scale programme in Nigeria found US$ 30 per DALY and US$ 1117 per life saved.

As noted in the WHO Guideline 2013 update, no cost data are available to allow comparison of the costs of treatment with F-100 therapeutic food product and with RUTF (*7*).

Availability

Currently, RUTF is provided by UNICEF for specific nutrition programmes; it is produced by manufacturers that have been approved by UNICEF.

Other considerations

N/A

Committee recommendations

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.

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Annex 1
WHO Model List of Essential Medicines (March 2017)

Explanatory notes

The core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **Complementary List** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The **square box symbol** (□) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square boxes are applicable to medicine selection for children — see the second EMLc for details.

Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The **[a]** symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

Where the ***[c]*** symbol is placed next to the Complementary List it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

Where the **[c]** symbol is placed next to an individual medicine or strength of medicine it signifies that there is a specific indication for restricting its use to children.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/.

Medicines and dosage forms are listed in alphabetical order within each section and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* http://www.who.int/medicines/publications/pharmacopoeia.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 Inhalational medicines

halothane	**Inhalation**.
isoflurane	**Inhalation**.
nitrous oxide	**Inhalation**.
oxygen	**Inhalation** (medical gas).

1.1.2 Injectable medicines

ketamine	**Injection:** 50 mg (as hydrochloride)/ mL in 10- mL vial.
propofol*	**Injection:** 10 mg/ mL; 20 mg/ mL. * Thiopental may be used as an alternative depending on local availability and cost.

1.2 Local anaesthetics

☐ bupivacaine	**Injection:** 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4- mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2- mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
Complementary List	
ephedrine	***Injection:** 30 mg (hydrochloride)/ mL in 1- mL ampoule.* *(For use in spinal anaesthesia during delivery, to prevent hypotension).*

1.3 Preoperative medication and sedation for short-term procedures

atropine	**Injection:** 1 mg (sulfate) in 1- mL ampoule.
☐ midazolam	**Injection:** 1 mg/ mL. **Oral liquid:** 2 mg/ mL [c]. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection:** 10 mg (sulfate or hydrochloride) in 1- mL ampoule.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*

1.4 Medical gases

oxygen*	**Inhalation** For use in the management of hypoxaemia. * No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE

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

acetylsalicylic acid	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg.
ibuprofen [a]	**Oral liquid:** 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol*	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Suppository:** 100 mg. **Tablet:** 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2.2 Opioid analgesics

codeine	**Tablet:** 30 mg (phosphate).
fentanyl*	**Transdermal patch:** 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr * For the management of cancer pain
☐ morphine*	**Granules (slow-release; to mix with water):** 20 mg –200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1- mL ampoule. **Oral liquid:** 10 mg (morphine hydrochloride or morphine sulfate)/5 mL. **Tablet (slow release):** 10 mg–200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate). * Alternatives limited to hydromorphone and oxycodone

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
Complementary List	*Tablet: 5 mg; 10 mg (as hydrochloride)*
*methadone**	***Oral liquid:*** *5mg/ 5mL; 10mg/ 5mL (as hydrochloride)*
	Concentrate for oral liquid: *5 mg/ mL; 10mg/ mL (as hydrochloride)*
	** For the management of cancer pain.*

2.3 Medicines for other common symptoms in palliative care	
amitriptyline	**Tablet:** 10 mg; 25 mg; 75 mg.
cyclizine [c]	**Injection:** 50 mg/ mL.
	Tablet: 50 mg.
dexamethasone	**Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).
	Oral liquid: 2 mg/5 mL.
	Tablet: 2 mg [c]; 4 mg.
diazepam	**Injection:** 5 mg/ mL.
	Oral liquid: 2 mg/5 mL.
	Rectal solution: 2.5 mg; 5 mg; 10 mg.
	Tablet: 5 mg; 10 mg.
docusate sodium	**Capsule:** 100 mg.
	Oral liquid: 50 mg/5 mL.
fluoxetine [a]	**Solid oral dosage form:** 20 mg (as hydrochloride).
	[a] >8 years.
haloperidol	**Injection:** 5 mg in 1- mL ampoule.
	Oral liquid: 2 mg/ mL.
	Solid oral dosage form: 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	**Injection:** 20 mg/ mL.
hyoscine hydrobromide [c]	**Injection:** 400 micrograms/ mL; 600 micrograms/ mL.
	Transdermal patches: 1 mg/72 hours.
lactulose [c]	**Oral liquid:** 3.1–3.7 g/5 mL.
loperamide	**Solid oral dosage form:** 2 mg.
metoclopramide	**Injection:** 5 mg (hydrochloride)/mL in 2-mL ampoule.
	Oral liquid: 5 mg/5 mL.
	Solid oral form: 10 mg (hydrochloride).
midazolam	**Injection:** 1 mg/ mL; 5 mg/ mL.
	Solid oral dosage form: 7.5 mg; 15 mg.
	Oral liquid: 2mg/ mL [c].

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
ondansetron [c] [a]	**Injection:** 2 mg base/ mL in 2- mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] >1 month.
senna	**Oral liquid:** 7.5 mg/5 mL.
3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	**Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1- mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.
☐ loratadine *	**Oral liquid:** 1 mg/ mL. **Tablet:** 10 mg. * There may be a role for sedating antihistamines for limited indications (EMLc).
☐ prednisolone	**Oral liquid:** 5 mg/ mL [c]. **Tablet:** 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Powder.**
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/ mL in 10- mL ampoule. **Oral liquid:** 10% [c]; 20% [c].
atropine	**Injection:** 1 mg (sulfate) in 1- mL ampoule.
calcium gluconate	**Injection:** 100 mg/ mL in 10- mL ampoule.
methylthioninium chloride (methylene blue)	**Injection:** 10 mg/ mL in 10- mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1- mL ampoule.
penicillamine	**Solid oral dosage form:** 250 mg.
potassium ferric hexacyano-ferrate(II) -2H2O(Prussian blue)	**Powder for oral administration.**
sodium nitrite	**Injection:** 30 mg/ mL in 10- mL ampoule.
sodium thiosulfate	**Injection:** 250 mg/ mL in 50- mL ampoule.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS *(continued)*	
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:*** *50 mg/ mL in 2- mL ampoule.*
fomepizole	***Injection:*** *5 mg/ mL (sulfate) in 20- mL ampoule or 1 g/ mL (base) in 1.5- mL ampoule.*
sodium calcium edetate	***Injection:*** *200 mg/ mL in 5- mL ampoule.*
succimer	***Solid oral dosage form:*** *100 mg.*

5. ANTICONVULSANTS/ANTIEPILEPTICS	
carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg.
diazepam	**Gel or rectal solution:** 5 mg/ mL in 0.5 mL; 2- mL; 4- mL tubes.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. * as adjunctive therapy for treatment-resistant partial or generalized seizures.
☐ lorazepam	**Parenteral formulation:** 2 mg/ mL in 1- mL ampoule; 4 mg/ mL in 1- mL ampoule.
magnesium sulfate*	**Injection:** 0.5g/ mL in 2- mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5g/ mL in 10- mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume). * For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
midazolam	**Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL **Ampoule*:** 1 mg/ mL; 10 mg/mL * For buccal administration when solution for oromucosal administration is not available
phenobarbital	**Injection:** 200 mg/ mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/ mL in 5- mL vial (sodium salt). **Oral liquid:** 25 mg to 30 mg/5 mL.* **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium salt). **Tablet (chewable):** 50 mg. * The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.

5. ANTICONVULSANTS/ANTIEPILEPTICS *(continued)*

valproic acid (sodium valproate)	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate).
Complementary List	
ethosuximide	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*
valproic acid (sodium valproate)	***Injection:*** *100 mg/ mL in 4- mL ampoule; 100 mg/ mL in 10- mL ampoule.*

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

albendazole	**Tablet (chewable):** 400 mg.
ivermectin	**Tablet (scored):** 3 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 600 mg.
pyrantel	**Oral liquid:** 50 mg (as embonate or pamoate)/ mL. **Tablet (chewable):** 250 mg (as embonate or pamoate).

6.1.2 Antifilarials

albendazole	**Tablet (chewable):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet (scored):** 3 mg.

6.1.3 Antischistosomals and other antitrematode medicines

praziquantel	**Tablet:** 600 mg.
triclabendazole	**Tablet:** 250 mg.
Complementary List	
*oxamniquine**	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.* ** Oxamniquine is listed for use when praziquantel treatment fails.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, three different categories were developed – ACCESS, WATCH and RESERVE groups.

Group 1 - KEY ACCESS ANTIBIOTICS

To improve both access and clinical outcomes antibiotics that were first or second choice antibiotics in at least one of the reviewed syndromes are designated as key ACCESS antibiotics, emphasizing their role as the antibiotics that should be widely available, affordable and quality-assured. ACCESS antibiotics are listed below. Selected ACCESS antibiotics may also be included in the WATCH group.

6.2.1 Beta-lactam medicines		***6.2.2 Other antibacterials***	
amoxicillin	cefotaxime*	amikacin	gentamicin
amoxicillin + clavulanic acid	ceftriaxone*	azithromycin*	metronidazole
ampicillin	cloxacillin	chloramphenicol	nitrofurantoin
benzathine benzylpenicillin	phenoxymethylpenicillin	ciprofloxacin*	spectinomycin (EML only)
benzylpenicillin	piperacillin + tazobactam*	clarithromycin*	sulfamethoxazole + trimethoprim
cefalexin	procaine benzyl penicillin	clindamycin	vancomycin (oral)*
cefazolin	*meropenem**	doxycycline	*vancomycin (parenteral)**
cefixime*			

Italics = Complementary List

*Watch group antibiotics included in the EML/EMLc only for specific, limited indications

The 2017 Expert Committee identified the following antibiotics or antibiotic classes that should be the subject of a specific stewardship focus. Antibiotics or antibiotic classes in these groups are designated accordingly in the EML/EMLc. The "WATCH" and "RESERVE" stewardship groups could assist in activities such as local, national and global monitoring of use; development of guidelines and educational activities.

6. ANTI-INFECTIVE MEDICINES *(continued)*

Group 2 - WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and so are recommended as first or second choice treatments only for a specific, limited number of indications. These medicines should be prioritized as key targets of stewardship programs and monitoring.

This group includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine[1] and/or antibiotics that are at relatively high risk of selection of bacterial resistance.

Watch group antibiotics
Quinolones and fluoroquinolones e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
3rd-generation cephalosporins (with or without beta-lactamase inhibitor) e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime
Macrolides e.g. azithromycin, clarithromycin, erythromycin
Glycopeptides e.g. teicoplanin, vancomycin
Antipseudomonal penicillins + beta-lactamase inhibitor e.g. piperacillin-tazobactam
Carbapenems e.g. meropenem, imipenem + cilastatin
Penems e.g. faropenem

Group 3 - RESERVE GROUP ANTIBIOTICS

This group includes antibiotics that should be treated as “last resort” options that should be accessible, but whose use should be tailored to highly specific patients and settings, when all alternatives have failed (e.g., serious, life-threatening infections due to multi-drug resistant bacteria). These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

1. http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1

6. ANTI-INFECTIVE MEDICINES *(continued)*

Reserve group antibiotics	
Aztreonam	Fosfomycin (IV)
4th generation cephalosporins e.g. cefepime	Oxazolidinones e.g. linezolid
5th generation cephalosporins e.g. ceftaroline	Tigecycline
Polymyxins e.g. polymyxin B, colistin	Daptomycin

6.2.1 Beta-lactam medicines

amoxicillin	**Powder for oral liquid:** 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL [c]. **Solid oral dosage form:** 250 mg; 500 mg (as trihydrate). **Powder for injection:** 250 mg; 500 mg; 1 g (as sodium) in vial.	
	FIRST CHOICE *- community acquired pneumonia (mild to moderate)* *- community acquired pneumonia (severe)* [c] *- complicated severe acute malnutrition* [c] - exacerbations of COPD *- lower urinary tract infections* *- otitis media* *- pharyngitis* *- sepsis in neonates and children* [c] *- sinusitis* *- uncomplicated severe acute malnutrition* [c]	**SECOND CHOICE** *- acute bacterial meningitis*
amoxicillin + clavulanic acid	**Oral liquid:** 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL [c]. **Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt). **Powder for injection:** 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.	

6. ANTI-INFECTIVE MEDICINES *(continued)*		
	FIRST CHOICE	**SECOND CHOICE**
	- community acquired pneumonia (severe) **[c]** *- complicated intraabdominal infections (mild to moderate)* *- exacerbations of COPD* *- hospital acquired pneumonia* *- low-risk febrile neutropenia* *- lower urinary tract infections* *- sinusitis* *- skin and soft tissue infections*	*- bone and joint infections* *- community-acquired pneumonia (mild to moderate)* *- community acquired pneumonia (severe)* *- otitis media*
ampicillin	**Powder for injection:** 500 mg; 1 g (as sodium salt) in vial.	
	FIRST CHOICE	**SECOND CHOICE**
	- community acquired pneumonia (severe) **[c]** *- complicated severe acute malnutrition* **[c]** *- sepsis in neonates and children* **[c]**	*- acute bacterial meningitis*
benzathine benzylpenicillin	**Powder for injection:** 900 mg benzylpenicillin (= 1.2 million IU) in 5- mL vial **[c]** ; 1.44 g benzylpenicillin (= 2.4 million IU) in 5- mL vial.	
	FIRST CHOICE	**SECOND CHOICE**
	- syphilis	
benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	
	FIRST CHOICE	**SECOND CHOICE**
	-community acquired pneumonia (severe) **[c]** *- complicated severe acute malnutrition* **[c]** *- sepsis in neonates and children* **[c]** *- syphilis*	*- acute bacterial meningitis* **[c]**

6. ANTI-INFECTIVE MEDICINES *(continued)*

cefalexin	**Powder for reconstitution with water:** 125 mg/5 mL; 250 mg/5 mL (anhydrous). **Solid oral dosage form:** 250 mg (as monohydrate).	
	FIRST CHOICE	**SECOND CHOICE** *- exacerbations of COPD* *- pharyngitis* *- skin and soft tissue infections*
cefazolin* [a]	**Powder for injection:** 1 g (as sodium salt) in vial. * also indicated for surgical prophylaxis. [a] >1 month.	
	FIRST CHOICE	**SECOND CHOICE** *- bone and joint infections*
cefixime WATCH GROUP	**Capsule or tablet:** 200 mg; 400 mg (as trihydrate). **Powder for oral liquid:** 100 mg /5 mL [c]	
	FIRST CHOICE	**SECOND CHOICE** *- acute invasive bacterial diarrhoea / dysentery* *- Neisseria gonorrhoeae*
cefotaxime* WATCH GROUP	**Powder for injection:** 250 mg per vial (as sodium salt) * 3rd generation cephalosporin of choice for use in hospitalized neonates.	
	FIRST CHOICE *- acute bacterial meningitis* *-community acquired pneumonia (severe)* *- complicated intraabdominal infections (mild to moderate)* *- complicated intrabdominal infections (severe)* *- hospital acquired pneumonia* *-pyelonephritis or prostatitis (severe)*	**SECOND CHOICE** *- bone and joint infections* *-pyelonephritis or prostatitis (mild to moderate)* *- sepsis in neonates and children* [c]

6. ANTI-INFECTIVE MEDICINES *(continued)*

ceftriaxone* [a]
WATCH GROUP

Powder for injection: 250 mg; 1 g (as sodium salt) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] >41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
- acute bacterial meningitis *-community acquired pneumonia (severe)* *- complicated intraabdominal infections (mild to moderate)* *- complicated intrabdominal infections (severe)* *- hospital acquired pneumonia* *- Neisseria gonorrhoeae* *-pyelonephritis or prostatitis (severe)*	*- acute invasive bacterial diarrhoea / dysentery* *- bone and joint infections* *- pyelonephritis or prostatitis (mild to moderate)* *- sepsis in neonates and children* [c]

☐ cloxacillin*

Capsule: 500 mg; 1 g (as sodium salt).

Powder for injection: 500 mg (as sodium salt) in vial.

Powder for oral liquid: 125 mg (as sodium salt)/5 mL.

*cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
- bone and joint infections *- skin and soft tissue infections*	*- sepsis in neonates and children* [c]

phenoxymethylpenicillin

Powder for oral liquid: 250 mg (as potassium salt)/5 mL.

Tablet: 250 mg (as potassium salt).

FIRST CHOICE	SECOND CHOICE
- community acquired pneumonia (mild to moderate) *- pharyngitis*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

piperacillin + tazobactam WATCH GROUP	**Powder for injection:** 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as sodium salt) + 500 mg (as sodium salt) in vial	
	FIRST CHOICE *- complicated intraabdominal infections (severe)* *- high-risk febrile neutropenia* *- hospital acquired pneumonia*	**SECOND CHOICE**
procaine benzylpenicillin*	**Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial. * Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.	
	FIRST CHOICE *- syphilis* [c]	**SECOND CHOICE** *- syphilis*
Complementary List		
ceftazidime *WATCH GROUP*	***Powder for injection:** 250 mg or 1 g (as pentahydrate) in vial.*	
*meropenem** [a] *WATCH GROUP*	***Powder for injection:** 500 mg (as trihydrate); 1 g (as trihydrate) in vial* [a] *>3 months.* **imipenem + cilastatin is an alternative except for acute bacterial meningitis where meropenem is preferred.*	
	FIRST CHOICE	**SECOND CHOICE** *- acute bacterial meningitis in neonates* [c] *- complicated intraabdominal infections (severe)* *- high-risk febrile neutropenia*
Complementary List – RESERVE GROUP		
aztreonam	***Powder for injection:** 1 g; 2 g in vial*	
fifth generation cephalosporins (with or without beta-lactamase inhibitor) e.g, ceftaroline	***Powder for injection**: 400 mg; 600 mg (as fosamil) in vial*	
fourth generation cephalosporins (with or without beta-lactamase inhibitor) e.g. cefepime	***Powder for injection:** 500 mg; 1g; 2g (as hydrochloride) in vial*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.2 Other antibacterials

amikacin	**Injection:** 250 mg (as sulfate)/mL in 2- mL vial	
	FIRST CHOICE *- pyelonephritis or prostatitis (severe)*	**SECOND CHOICE** *- high-risk febrile neutropenia* *- sepsis in neonates and children* [C]
azithromycin* WATCH GROUP	**Capsule:** 250 mg; 500 mg (anhydrous). **Oral liquid:** 200 mg/5 mL. * also listed for single-dose treatment of trachoma and yaws.	
	FIRST CHOICE *- Chlamydia trachomatis* *- cholera* [C] *- Neisseria gonorrhoeae*	**SECOND CHOICE** *- acute invasive bacterial diarrhoea / dysentery* *- Neisseria gonorrhoeae*
chloramphenicol	**Capsule:** *250 mg.* **Oily suspension for injection***: 0.5 g (as sodium succinate)/ mL in 2- mL ampoule. * Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults. **Oral liquid:** 150 mg (as palmitate)/5 mL. **Powder for injection:** 1 g (sodium succinate) in vial.	
	FIRST CHOICE	**SECOND CHOICE** *- acute bacterial meningitis*
ciprofloxacin WATCH GROUP	**Oral liquid:** 250 mg/5 mL (anhydrous) [C]. **Solution for IV infusion:** 2 mg/ mL (as hyclate) [C]. **Tablet:** 250 mg (as hydrochloride).	
	FIRST CHOICE *- acute invasive bacterial diarrhoea / dysentery* *- low-risk febrile neutropenia* *- pyelonephritis or prostatitis (mild to moderate)*	**SECOND CHOICE** *- cholera* *- complicated intraabdominal infections (mild to moderate)*

6. ANTI-INFECTIVE MEDICINES *(continued)*

clarithromycin*†
WATCH GROUP

Solid oral dosage form: 500 mg.

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL

Powder for injection: 500 mg in vial

*erythromycin may be an alternative.

†clarithromycin is also listed for use in combination regimens for eradication of *H. pylori* in adults.

FIRST CHOICE	SECOND CHOICE
-community acquired pneumonia (severe)	*- pharyngitis*

clindamycin

Capsule: 150 mg (as hydrochloride).

Injection: 150 mg (as phosphate)/ mL.

Oral liquid: 75 mg/5 mL (as palmitate) [C]

FIRST CHOICE	SECOND CHOICE
	- bone and joint infections

doxycycline [a]

Oral liquid: 25 mg/5 mL [C]; 50 mg/5 mL (anhydrous) [C].

Solid oral dosage form: 50 mg [C]; 100 mg (as hyclate).

Powder for injection: 100 mg in vial

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

FIRST CHOICE	SECOND CHOICE
- Chlamydia trachomatis	*- cholera* [C]
- cholera	*-community acquired pneumonia (mild to moderate)*
	- exacerbations of COPD

gentamicin

Injection: 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial.

FIRST CHOICE	SECOND CHOICE
- community acquired pneumonia (severe) [C]	*- Neisseria gonorrhoeae*
- complicated severe acute malnutrition [C]	
- sepsis in neonates and children [C]	

6. ANTI-INFECTIVE MEDICINES *(continued)*

metronidazole	**Injection:** 500 mg in 100- mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Suppository:** 500 mg; 1 g. **Tablet:** 200 mg to 500 mg.	
	FIRST CHOICE *- C. difficile infection* *- complicated intraabdominal infections (mild to moderate)* *- complicated intrabdominal infections (severe)* *- Trichomonas vaginalis*	**SECOND CHOICE** *- complicated intraabdominal infections (mild to moderate)*
nitrofurantoin	**Oral liquid:** 25 mg/5 mL [C]. **Tablet:** 100 mg.	
	FIRST CHOICE *- lower urinary tract infections*	**SECOND CHOICE**
spectinomycin	**Powder for injection:** 2 g (as hydrochloride) in vial.	
	FIRST CHOICE	**SECOND CHOICE** *- Neisseria gonorrhoeae*
sulfamethoxazole + trimethoprim*	**Injection:** 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg. *single agent trimethoprim may be an alternative for lower urinary tract infection.	
	FIRST CHOICE *- lower urinary tract infections*	**SECOND CHOICE** *- acute invasive diarrhoea / bacterial dysentery*
vancomycin WATCH GROUP	**Capsule:** 125 mg; 250 mg (as hydrochloride).	
		SECOND CHOICE *- C. difficile infection*

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

vancomycin	***Powder for injection:*** *250 mg (as hydrochloride) in vial.*
WATCH GROUP	**FIRST CHOICE** / **SECOND CHOICE** *-high-risk febrile neutropenia*

Complementary List – RESERVE GROUP

daptomycin	***Powder for injection:*** *350 mg; 500 mg in vial*
fosfomycin	***Powder for injection:*** *2 g; 4 g (as sodium) in vial*
oxazolindinones *e.g., linezolid*	***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *400 mg; 600 mg.*
polymyxins *e.g., colistin*	***Powder for injection:*** *1 million I.U. (as colistemethate sodium) in vial*
tigecycline	***Powder for injection:*** *50 mg in vial*

6.2.3 Antileprosy medicines

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Capsule:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Solid oral dosage form:** 150 mg; 300 mg.

6.2.4 Antituberculosis medicines

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	**Oral liquid:** 25 mg/ mL [c]. **Tablet:** 100 mg to 400 mg (hydrochloride).
ethambutol + isoniazid	**Tablet:** 400 mg + 150 mg.
ethambutol + isoniazid + pyrazinamide + rifampicin	**Tablet:** 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	**Tablet:** 275 mg + 75 mg + 150 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

isoniazid	**Oral liquid:** 50 mg/5 mL [c]. **Tablet:** 100 mg to 300 mg. **Tablet (scored):** 50 mg.
isoniazid + pyrazinamide + rifampicin	**Tablet:** 75 mg + 400 mg + 150 mg. 150 mg + 500 mg + 150 mg (For intermittent use three times weekly). **Tablet (dispersible):** 50 mg + 150 mg + 75 mg [c].
isoniazid + rifampicin	**Tablet:** 75 mg + 150 mg; 150 mg + 300 mg. 60 mg + 60 mg (**For intermittent use three times weekly**). 150 mg + 150 mg (**For intermittent use three times weekly**). **Tablet (dispersible)**: 50 mg + 75 mg [c].
pyrazinamide	**Oral liquid:** 30 mg/ mL [c]. **Tablet:** 400 mg. **Tablet (dispersible):** 150 mg. **Tablet (scored):** 150 mg.
rifabutin	**Capsule:** 150 mg.* * For use only in patients with HIV receiving protease inhibitors.
rifampicin	**Oral liquid:** 20 mg/ mL [c]. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine*	**Tablet:** 150 mg *For treatment of latent TB infection (LTBI) only

Complementary List

Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin	***Powder for injection:*** *100 mg; 500 mg; 1 g (as sulfate) in vial.*
bedaquiline	***Tablet:*** *100 mg.*
capreomycin	***Powder for injection:*** *1 g (as sulfate) in vial.*
clofazimine	***Capsule:*** *50 mg; 100 mg.*
*cycloserine**	***Solid oral dosage form:*** *250 mg.* **Terizidone may be an alternative*

6. ANTI-INFECTIVE MEDICINES *(continued)*

delamanid [a]	***Tablet:*** *50 mg.* [a] >6 years
*ethionamide**	***Tablet:*** *125 mg; 250 mg.* **Protionamide may be an alternative.*
kanamycin	***Powder for injection:*** *1 g (as sulfate) in vial.*
levofloxacin	***Tablet:*** *250mg; 500 mg; 750 mg.*
linezolid	***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *400 mg; 600 mg.*
moxifloxacin	***Tablet:*** *400 mg.*
p-aminosalicylic acid	***Granules:*** *4 g in sachet.* ***Tablet:*** *500 mg.*
streptomycin [c]	***Powder for injection:*** 1 g (as sulfate) in vial.

6.3 Antifungal medicines

amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
clotrimazole	**Vaginal cream:** 1%; 10%. **Vaginal tablet:** 100 mg; 500 mg.
fluconazole	**Capsule:** 50 mg. **Injection:** 2 mg/ mL in vial. **Oral liquid:** 50 mg/5 mL.
flucytosine	**Capsule:** 250 mg. **Infusion:** 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL [c]. **Solid oral dosage form:** 125 mg; 250 mg.
itraconazole*	**Capsule:** 100 mg. **Oral liquid:** 10 mg/mL. * For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 50 mg/5 mL [c] ; 100 000 IU/ mL [c]. **Pessary:** 100 000 IU. **Tablet:** 100 000 IU; 500 000 IU.
voriconazole*	**Tablet:** 50 mg; 200 mg **Powder for injection:** 200 mg in vial **Powder for oral liquid:** 40 mg/mL *For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.
Complementary List	
potassium iodide	***Saturated solution.***

6.4 Antiviral medicines

6.4.1 Antiherpes medicines

☐ aciclovir	**Oral liquid:** 200 mg/5 mL [c] **Powder for injection:** 250 mg (as sodium salt) in vial. **Tablet:** 200 mg.

6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following three classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission, pre-exposure prophylaxis (where indicated) and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

abacavir (ABC)	**Tablet:** 300 mg (as sulfate). **Tablet (dispersible, scored):** 60 mg (as sulfate) [c]
lamivudine (3TC)	**Oral liquid:** 50 mg/5 mL [c]. **Tablet:** 150 mg.
tenofovir disoproxil fumarate† (TDF)	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). †also indicated for pre-exposure prophylaxis.

6. ANTI-INFECTIVE MEDICINES *(continued)*

zidovudine (ZDV or AZT)	**Capsule:** 250 mg. **Oral liquid:** 50 mg/5 mL. **Solution for IV infusion injection:** 10 mg/ mL in 20- mL vial. **Tablet:** 300 mg. **Tablet (dispersible, scored):** 60 mg [c].

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ) [a]	**Tablet:** 200 mg (scored); 600 mg. [a] >3 years or >10 kg weight.
nevirapine (NVP) [a]	**Oral liquid:** 50 mg/5 mL. **Tablet:** 50 mg (dispersible); 200 mg. [a] > 6 weeks

6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir [a]	**Solid oral dosage form:** 100 mg; 300 mg (as sulfate). [a] >25 kg.
atazanavir + ritonavir	**Tablet (heat stable):** 300 mg (as sulfate) + 100 mg.
darunavir [a]	**Tablet:** 75 mg; 400 mg; 600 mg; 800 mg [a] >3 years
lopinavir + ritonavir (LPV/r)	**Oral liquid:** 400 mg + 100 mg/5 mL. **Tablet (heat stable):** 100 mg + 25 mg; 200 mg + 50 mg. **Capsule containing oral pellets:** 40 mg + 10 mg [c].
ritonavir	**Oral liquid:** 400 mg/5 mL. **Tablet (heat stable):** 25 mg; 100 mg.

6.4.2.4 Integrase inhibitors

dolutegravir	**Tablet:** 50 mg
raltegravir*	**Tablet (chewable):** 25 mg; 100 mg. **Tablet:** 400 mg *for use in pregnant women and in second-line regimens in accordance with WHO treatement guidelines.

6. ANTI-INFECTIVE MEDICINES *(continued)*

FIXED-DOSE COMBINATIONS

abacavir + lamivudine	**Tablet (dispersible, scored):** 60 mg (as sulfate) + 30 mg; 120 mg (as sulfate) + 60 mg.
efavirenz + emtricitabine* + tenofovir	**Tablet:** 600 mg + 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil). *Emtricitabine (FTC) is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.
efavirenz + lamivudine + tenofovir	**Tablet:** 400 mg + 300 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
emtricitabine* + tenofovir†	**Tablet:** 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil). *Emtricitabine (FTC) is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals. † combination also indicated for pre-exposure prophylaxis
lamivudine + nevirapine + zidovudine	**Tablet:** 30 mg + 50 mg + 60 mg [C]; 150 mg + 200 mg + 300 mg.
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg [C]; 150 mg + 300 mg.

6.4.2.5 Medicines for prevention of HIV-related opportunistic infections

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg

6.4.3 Other antivirals

ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10- mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of viral haemorrhagic fevers
valganciclovir*	**Tablet:** 450 mg. *For the treatment of cytomegalovirus retinitis (CMVr).
Complementary List	
*oseltamivir**	***Capsule:*** *30 mg; 45 mg; 75 mg (as phosphate).* ***Oral powder:*** *12 mg/ mL.* ** severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4 Antihepatitis medicines

6.4.4.1 Medicines for hepatitis B

6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

entecavir	**Oral liquid:** 0.05 mg/ mL **Tablet:** 0.5 mg; 1 mg
tenofovir disoproxil fumarate (TDF)	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).

6.4.4.2 Medicines for hepatitis C

Based on current evidence, medicines in the following classes of direct acting antiviral medicines are included as essential medicines for treatment of hepatitis C virus infection. WHO guidelines recommend specific combination therapy utilizing medicines from different classes.

6.4.4.2.1 Nucleotide polymerase inhibitors

sofosbuvir	**Tablet:** 400 mg

6.4.4.2.2 Protease inhibitors

simeprevir	**Capsule:** 150 mg

6.4.4.2.3 NS5A inhibitors

daclatasvir	**Tablet:** 30 mg; 60 mg (as hydrochloride)

6.4.4.2.4 Non-nucleoside polymerase inhibitors

dasabuvir	**Tablet:** 250 mg

6.4.4.2.5 Other antivirals

ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10- mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of hepatitis C, in combination with peginterferon and/or direct acting anti-viral medicines
Complementary List	
*pegylated interferon alfa (2a or 2b) **	***Vial or prefilled syringe:*** *180 micrograms (peginterferon alfa-2a),* *80 microgram, 100 microgram (peginterferon alfa-2b).* ** To be used in combination with ribavirin.*

FIXED-DOSE COMBINATIONS

Alternative combinations of DAAs from different pharmacological classes are possible.

ledipasvir + sofosbuvir	**Tablet:** 90 mg + 400 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

ombitasvir + paritaprevir + ritonavir	**Tablet:** 12.5 mg + 75 mg + 50 mg
sofosbuvir + velpatasvir	**Tablet:** 400 mg + 100 mg

6.5 Antiprotozoal medicines

6.5.1 Antiamoebic and antigiardiasis medicines

diloxanide [a]	**Tablet:** 500 mg (furoate). [a] >25 kg.
☐ metronidazole	**Injection:** 500 mg in 100- mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Tablet:** 200 mg to 500 mg.

6.5.2 Antileishmaniasis medicines

amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as the sulfate).
sodium stibogluconate or meglumine antimoniate	**Injection:** 100 mg/ mL, 1 vial = 30 mL or 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5- mL ampoule.

6.5.3 Antimalarial medicines

6.5.3.1 For curative treatment

Medicines for the treatment of P. falciparum malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs) in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
artemether*	**Oily injection:** 80 mg/ mL in 1- mL ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg [c]. * Not recommended in the first trimester of pregnancy or in children below 5 kg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Rectal dosage form:** 50 mg [c]; 100 mg [c]; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [c]. **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
artesunate + amodiaquine*	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. * Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
artesunate + pyronaridine tetraphosphate [a]	**Tablet:** 60 mg + 180 mg **Granules:** 20 mg + 60 mg [c]. [a] > 5 kg
chloroquine*	**Oral liquid:** 50 mg (as phosphate or sulfate)/5 mL. **Tablet:** 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of P.vivax infection.
dihydroartemisinin + piperaquine phosphate [a]	**Tablet:** 20 mg + 160 mg; 40 mg + 320 mg [a] > 5 kg
doxycycline*	**Capsule:** 100 mg (as hydrochloride or hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of P.vivax and P.ovale infections, given for 14 days.
quinine*	**Injection:** 300 mg quinine hydrochloride/ mL in 2- mL ampoule. **Tablet:** 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.

6. ANTI-INFECTIVE MEDICINES *(continued)*

sulfadoxine + pyrimethamine*	**Tablet:** 500 mg + 25 mg. * Only in combination with artesunate 50 mg.

6.5.3.2 For prophylaxis

chloroquine*	**Oral liquid:** 50 mg (as phosphate or sulfate)/5 mL. **Tablet:** 150 mg (as phosphate or sulfate). * For use only in central American regions, for P.vivax infections.
doxycycline [a]	**Solid oral dosage form:** 100 mg (as hydrochloride or hyclate). [a] >8 years.
mefloquine [a]	**Tablet:** 250 mg (as hydrochloride). [a] >5 kg or >3 months.
proguanil*	**Tablet:** 100 mg (as hydrochloride). * For use only in combination with chloroquine.

6.5.4 Antipneumocystosis and antitoxoplasmosis medicines

pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL [c]. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg [c].
Complementary List	
pentamidine	***Tablet:** 200 mg; 300 mg (as isethionate).*

6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine*	**Powder for injection:** 200 mg (as isetionate) in vial. * To be used for the treatment of Trypanosoma brucei gambiense infection.
suramin sodium*	**Powder for injection:** 1 g in vial. * To be used for the treatment of the initial phase of Trypanosoma brucei rhodesiense infection.

6. ANTI-INFECTIVE MEDICINES *(continued)*

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg (hydrochloride)/ mL in 100- mL bottle. * To be used for the treatment of Trypanosoma brucei gambiense infection.
melarsoprol	**Injection:** 3.6% solution, 5- mL ampoule (180 mg of active compound).
nifurtimox*	**Tablet:** 120 mg. * Only to be used in combination with eflornithine, for the treatment of Trypanosoma brucei gambiense infection.

Complementary List [c]

melarsoprol	***Injection:** 3.6% solution in 5- mL ampoule (180 mg of active compound).*

6.5.5.2 American trypanosomiasis

benznidazole	**Tablet:** 12.5 mg [c];100 mg. **Tablet (scored):** 50 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg; 250 mg.

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

acetylsalicylic acid	**Tablet:** 300 mg to 500 mg.
ibuprofen [c]	**Tablet:** 200 mg; 400 mg.
paracetamol	**Oral liquid:** 120 mg/5 mL [c]; 125 mg/5 mL [c]. **Tablet:** 300 mg to 500 mg.

7.2 For prophylaxis

☐ propranolol	**Tablet:** 20 mg; 40 mg (hydrochloride).

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES

Medicines listed below should be used according to protocols for treatment of the diseases.

8.1 Immunosuppressive medicines

Complementary List

azathioprine	***Powder for injection:** 100 mg (as sodium salt) in vial.* ***Tablet (scored):** 50 mg.*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/ mL in 1- mL ampoule for organ transplantation.*
8.2 Cytotoxic and adjuvant medicines	
Complementary List	
all-trans retinoid acid (ATRA)	***Capsule:*** *10 mg.* - *Acute promyelocytic leukaemia.*
allopurinol [c]	***Tablet:*** *100 mg; 300 mg.*
asparaginase	***Powder for injection:*** *10 000 IU in vial.* - *Acute lymphoblastic leukaemia.*
bendamustine	***Injection:*** *45 mg/0.5 mL; 180 mg/2 mL.* - *Chronic lymphocytic leukaemia* - *Follicular lymphoma*
bleomycin	***Powder for injection:*** *15 mg (as sulfate) in vial.* - *Hodgkin lymphoma* - *Kaposi sarcoma* - *Ovarian germ cell tumour* - *Testicular germ cell tumour*
calcium folinate	***Injection*****:** *3 mg/ mL in 10- mL ampoule.* ***Tablet*****:** *15 mg.* - *Early stage colon cancer* - *Early stage rectal cancer* - *Gestational trophoblastic neoplasia* - *Metastatic colorectal cancer* - *Osteosarcoma* - *Burkitt lymphoma*
capecitabine	***Tablet*****:** *150 mg; 500 mg.* - Early stage colon cancer - Early stage rectal cancer - Metastatic breast cancer - Metastatic colorectal cancer

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* - *Early stage breast cancer* - *Epithelial ovarian cancer* - *Nasopharyngeal cancer* - *Non-small cell lung cancer* - *Osteosarcoma* - *Retinoblastoma*
chlorambucil	***Tablet:*** *2 mg.* - *Chronic lymphocytic leukaemia.*
cisplatin	***Injection:*** *50 mg/50 mL; 100 mg/100 mL.* - *Cervical cancer (as a radio-sensitizer)* - *Head and neck cancer (as a radio-sensitizer)* - *Nasopharyngeal cancer (as a radio-sensitizer)* - *Non-small cell lung cancer* - *Osteosarcoma* - *Ovarian germ cell tumour* - *Testicular germ cell tumour*
cyclophosphamide	***Powder for injection:*** *500 mg in vial.* ***Tablet:*** *25 mg.* - *Chronic lymphocytic leukaemia* - *Diffuse large B-cell lymphoma* - *Early stage breast cancer* - *Gestational trophoblastic neoplasia* - *Follicular lymphoma* - *Rhabdomyosarcoma* - *Ewing sarcoma* - *Acute lymphoblastic leukaemia* - *Burkitt lymphoma* - *Metastatic breast cancer*
cytarabine	***Powder for injection:*** *100 mg in vial.* - *Acute myelogenous leukaemia* - *Acute lymphoblastic leukaemia* - Acute promyelocytic leukaemia - Burkitt lymphoma.

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
dacarbazine	***Powder for injection:*** *100 mg in vial.* - *Hodgkin lymphoma*
dactinomycin	**Powder for injection:** *500 micrograms in vial.* - *Gestational trophoblastic neoplasia* - *Rhabdomyosarcoma* - *Wilms tumour*
dasatinib	***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.* - *Imatinib-resistant chronic myeloid leukaemia*
daunorubicin	***Powder for injection:*** *50 mg (hydrochloride) in vial.* - *Acute lymphoblastic leukaemia* - *Acute myelogenous leukaemia* - *Acute promyelocytic leukaemia*
docetaxel	***Injection:*** *20 mg/ mL; 40 mg/ mL.* - *Early stage breast cancer* - *Metastatic breast cancer* - *Metastatic prostate cancer*
doxorubicin	***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* - *Diffuse large B-cell lymphoma* - *Early stage breast cancer* - *Hodgkin lymphoma* - *Kaposi sarcoma* - *Follicular lymphoma* - *Metastatic breast cancer* - *Osteosarcoma* - *Ewing sarcoma* - *Acute lymphoblastic leukaemia* - *Wilms tumour* - *Burkitt lymphoma*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*

etoposide	***Capsule:*** *100 mg.* ***Injection:*** 20 mg/ mL in 5- mL ampoule. - Testicular germ cell tumour - Gestational trophoblastic neoplasia - Hodgkin lymphoma - *Non-small cell lung cancer* - *Ovarian germ cell tumour* - *Retinoblastoma* - *Ewing sarcoma* - *Acute lymphoblastic leukaemia* - *Burkitt lymphoma*
filgrastim	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe 300 micrograms/mL in 1- mL vial, 480 mg/1.6 mL in 1.6- mL vial.* - *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.* - *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* - *To facilitate administration of dose dense chemotherapy regimens*
fludarabine	***Powder for injection:*** *50 mg (phosphate) in vial.* ***Tablet:*** *10 mg* - *Chronic lymphocytic leukaemia.*
fluorouracil	***Injection:*** *50 mg/ mL in 5- mL ampoule.* - *Early stage breast cancer* - *Early stage colon cancer* - *Early stage rectal cancer* - *Metastatic colorectal cancer* - *Nasopharyngeal cancer.*
gemcitabine	***Powder for injection:*** *200 mg in vial, 1 g in vial.* - *Epithelial ovarian cancer* - *Non-small cell lung cancer*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.* - *Chronic myeloid leukaemia.*
ifosfamide	***Powder for injection:*** *500 mg vial; 1-g vial; 2-g vial.* - *Testicular germ cell tumour* - *Ovarian germ cell tumour* - *Osteosarcoma* - *Rhabdomyosarcoma* - *Ewing sarcoma*
imatinib	***Tablet:*** *100 mg; 400 mg.* - *Chronic myeloid leukaemia* - *Gastrointestinal stromal tumour*
irinotecan	***Injection:*** *40 mg/2 mL in 2- mL vial; 100 mg/5 mL in 5- mL vial; 500 mg/25 mL in 25- mL vial.* - *Metastatic colorectal cancer.*
mercaptopurine	***Tablet:*** *50 mg.* - *Acute lymphoblastic leukaemia* - *Acute promyelocytic leukaemia.*
mesna	***Injection:*** *100 mg/ mL in 4- mL and 10- mL ampoules.* ***Tablet:*** *400 mg; 600 mg.* - *Testicular germ cell tumour* - *Ovarian germ cell tumour* - *Osteosarcoma* - *Rhabdomyosarcoma* - *Ewing sarcoma.*
methotrexate	***Powder for injection: 5****0 mg (as sodium salt) in vial.* ***Tablet:*** *2.5 mg (as sodium salt).* - *Early stage breast cancer* - *Gestational trophoblastic neoplasia* - *Osteosarcoma* - *Acute lymphoblastic leukaemia* - *Acute promyelocytic leukaemia*
nilotinib	***Capsule:*** *150 mg; 200 mg.* - *Imatinib-resistant chronic myeloid leukaemia*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*

oxaliplatin	***Injection:*** *50 mg/10 mL in 10- mL vial; 100 mg/20 mL in 20- mL vial; 200 mg/40 mL in 40- mL vial.* ***Powder for injection:*** *50 mg, 100 mg in vial.* - *Early stage colon cancer* - *Metastatic colorectal cancer*
paclitaxel	***Powder for injection:*** *6 mg/ mL.* - *Epithelial ovarian cancer* - *Early stage breast cancer* - *Metastatic breast cancer* - *Kaposi sarcoma* - *Nasopharyngeal cancer* - *Non-small cell lung cancer* - *Ovarian germ cell tumour*
procarbazine	***Capsule:*** *50 mg (as hydrochloride).*
rituximab	***Injection:*** *100 mg/10 mL in 10- mL vial; 500 mg/50 mL in 50- mL vial.* - *Diffuse large B-cell lymphoma* - *Chronic lymphocytic leukaemia* - *Follicular lymphoma.*
tioguanine [c]	***Solid oral dosage form:*** *40 mg.* - *Acute lymphoblastic leukaemia.*
trastuzumab	***Powder for injection:*** *60 mg; 150 mg; 440 mg in vial* - *Early stage HER2 positive breast cancer* - *Metastatic HER2 positive breast cancer.*
vinblastine	***Powder for injection:*** *10 mg (sulfate) in vial.* - *Hodgkin lymphoma* - *Kaposi sarcoma.* - *Testicular germ cell tumour* - *Ovarian germ cell tumour*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
vincristine	***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* - *Diffuse large B-cell lymphoma* - *Gestational trophoblastic neoplasia* - *Hodgkin lymphoma* - *Kaposi sarcoma* - *Follicular lymphoma* - *Retinoblastoma* - *Rhabdomyosarcoma* - *Ewing sarcoma* - *Acute lymphoblastic leukaemia* - *Wilms tumour* - *Burkitt lymphoma.*
vinorelbine	***Injection:*** *10 mg/mL in 1- mL vial; 50 mg/5 mL in 5- mL vial.* - *Non-small cell lung cancer* - *Metastatic breast cancer*
zoledronic acid	***Concentrate solution for infusion:*** *4 mg/5 mL in 5- mL vial.* ***Solution for infusion:*** *4 mg/100 mL in 100- mL bottle.* - *Malignancy-related bone disease*
8.3 Hormones and antihormones	
Complementary List	
☐ *anastrozole*	***Tablet:*** *1 mg.* - *Early stage breast cancer* - *Metastatic breast cancer.*
☐ *bicalutamide*	***Tablet:*** *50 mg.* - *Metastatic prostate cancer.*
dexamethasone	***Injection:*** *4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).* ***Oral liquid:*** *2 mg/5 mL* [c]. - *Acute lymphoblastic leukaemia.*
☐ *leuprorelin*	***Dose form*** - *Early stage breast cancer* - *Metastatic prostate cancer*
hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* - *Acute lymphoblastic leukaemia.*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
methylprednisolone [C]	***Injection:*** *40 mg/ mL (as sodium succinate) in 1- mL single-dose vial and* *5- mL multi-dose vials; 80 mg/ mL (as sodium succinate) in 1- mL single-dose vial.* - *Acute lymphoblastic leukamia.*
☐ *prednisolone*	***Oral liquid:*** *5 mg/ mL* [C]. ***Tablet:*** *5 mg; 25 mg.* - *Chronic lymphocytic leukaemia* - *Diffuse large B-cell lymphoma* - *Hodgkin lymphoma* - *Follicular lymphoma* - *Acute lymphoblastic leukaemia* - *Burkitt lymphoma*
tamoxifen	***Tablet:*** *10 mg; 20 mg (as citrate).* - *Early stage breast cancer* - *Metastatic breast cancer*
9. ANTIPARKINSONISM MEDICINES	
☐ biperiden	**Injection:** 5 mg (lactate) in 1- mL ampoule. **Tablet:** 2 mg (hydrochloride).
levodopa + ☐ carbidopa	**Tablet:** 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg
10. MEDICINES AFFECTING THE BLOOD	
10.1 Antianaemia medicines	
ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/ mL. **Tablet:** equivalent to 60 mg iron.
ferrous salt + folic acid	**Tablet:** equivalent to 60 mg iron + 400 micrograms folic acid (nutritional supplement for use during pregnancy).
folic acid	**Tablet:** 400 micrograms*; 1 mg; 5 mg. *periconceptual use for prevention of first occurrence of neural tube defects
hydroxocobalamin	**Injection:** 1 mg (as acetate, as hydrochloride or as sulfate) in 1- mL ampoule.

10. MEDICINES AFFECTING THE BLOOD *(continued)*

Complementary List

☐ *erythropoiesis-stimulating agents**	***Injection: pre-filled syringe*** *1000IU/ 0.5 mL; 2000IU/ 0.5 mL; 3000IU/ 0.3 mL; 4000IU/ 0.4 mL; 5000IU/ 0.5 mL; 6000IU/ 0.6 mL; 8000IU/ 0.8mL; 10 000IU/ 1 mL; 20 000IU/ 0.5 mL; 40 000IU/ 1 mL* ** the square box applies to epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta,and their respective biosimilars.*

10.2 Medicines affecting coagulation

☐ enoxaparin*	**Injection: ampoule or pre-filled syringe** 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL *Alternatives are limited to nadroparin and dalteparin
heparin sodium	**Injection:** 1000 IU/ mL; 5000 IU/ mL; 20 000 IU/ mL in 1- mL ampoule.
phytomenadione	**Injection:** 1 mg/ mL [c]; 10 mg/ mL in 5- mL ampoule. Tablet: 10 mg.
protamine sulfate	**Injection:** 10 mg/ mL in 5- mL ampoule.
tranexamic acid	**Injection:** 100 mg/ mL in 10- mL ampoule.
☐ warfarin	**Tablet:** 1 mg; 2 mg; 5 mg (sodium salt).

Complementary List [c]

desmopressin	***Injection:*** *4 micrograms/ mL (as acetate) in 1- mL ampoule.* ***Nasal spray:*** *10 micrograms (as acetate) per dose*
heparin sodium	***Injection:*** *1000 IU/ mL; 5000 IU/ mL in 1- mL ampoule.*
protamine sulfate	***Injection:*** *10 mg/ mL in 5- mL ampoule.*
☐ *warfarin*	***Tablet:*** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).*

10.3 Other medicines for haemoglobinopathies

Complementary List

*deferoxamine**	***Powder for injection:*** *500 mg (mesilate) in vial.* ** Deferasirox oral form may be an alternative, depending on cost and availability.*
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 500 mg; 1 g.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh–frozen plasma

platelets

red blood cells

whole blood

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11.2.1 Human immunoglobulins

anti-D immunoglobulin	**Injection:** 250 micrograms in single-dose vial.
Anti-rabies immunoglobulin	**Injection:** 150 IU/ mL in vial.
Anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	
normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.** ***Intravenous administration:*** *5%; 10% protein solution.*** ***Subcutaneous administration:*** *15%; 16% protein solution.** ** Indicated for primary immune deficiency.* ***Indicated for primary immune deficiency and Kawasaki disease.*

11.2.2 Blood coagulation factors

Complementary List

☐ *coagulation factor VIII*	***Powder for injection:*** *500 IU/vial.*
☐ *coagulation factor IX*	***Powder for injection:*** *500 IU/vial, 1000 IU/vial.*

11.3 Plasma substitutes

☐ dextran 70*	**Injectable solution:** 6%. * Polygeline, injectable solution, 3.5% is considered as equivalent.

12. CARDIOVASCULAR MEDICINES

Fixed-dose combinations for non-communicable diseases may have advantages over the single medicines given concomitantly, including increased adherence and reduced pill burden. The potential value of fixed-dose combinations of currently listed essential medicines, with regulatory approval and demonstrated bioavailability for the management of chronic non-communicable diseases, is recognized.

12.1 Antianginal medicines

☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. * includes metoprolol and carvedilol as alternatives.
glyceryl trinitrate	**Tablet (sublingual):** 500 micrograms.
☐ isosorbide dinitrate	**Tablet (sublingual):** 5 mg.
verapamil	**Tablet:** 40 mg; 80 mg (hydrochloride).

12.2 Antiarrhythmic medicines

☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. * includes metoprolol and carvedilol as alternatives.
digoxin	**Injection:** 250 micrograms/ mL in 2- mL ampoule. Oral liquid: 50 micrograms/ mL. Tablet: 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	**Injection:** 100 micrograms/ mL (as acid tartrate or hydrochloride) in 10- mL ampoule.
lidocaine	**Injection:** 20 mg (hydrochloride)/ mL in 5- mL ampoule.
verapamil	**Injection:** 2.5 mg (hydrochloride)/ mL in 2- mL ampoule. **Tablet:** 40 mg; 80 mg (hydrochloride).
Complementary List	
amiodarone	***Injection:*** *50 mg/ mL in 3- mL ampoule (hydrochloride).* ***Tablet:*** *100 mg; 200 mg; 400 mg (hydrochloride).*

12.3 Antihypertensive medicines

☐ amlodipine	Tablet: 5 mg (as maleate, mesylate or besylate).
☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. * includes atenolol, metoprolol and carvedilol as alternatives. Atenolol should not be used as a first-line agent in uncomplicated hypertension in patients >60 years
☐ enalapril	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).

12. CARDIOVASCULAR MEDICINES *(continued)*	
hydralazine*	**Powder for injection:** 20 mg (hydrochloride) in ampoule. Tablet: 25 mg; 50 mg (hydrochloride). * Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
☐ hydrochlorothiazide	**Oral liquid:** 50 mg/5 mL. **Solid oral dosage form:** 12.5 mg; 25 mg.
methyldopa*	**Tablet:** 250 mg. * Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
☐ losartan	**Tablet:** 25 mg; 50 mg; 100 mg.
Complementary List	
sodium nitroprusside	***Powder for infusion:*** *50 mg in ampoule.*
12.4 Medicines used in heart failure	
☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. *includes metoprolol and carvedilol as alternatives.
digoxin	**Injection:** 250 micrograms/ mL in 2- mL ampoule. **Oral liquid:** 50 micrograms/ mL. **Tablet:** 62.5 micrograms; 250 micrograms.
☐ enalapril	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).
☐ furosemide	**Injection:** 10 mg/ mL in 2- mL ampoule. **Oral liquid:** 20 mg/5 mL [c]. **Tablet:** 40 mg.
☐ hydrochlorothiazide	**Oral liquid:** 50 mg/5 mL. **Solid oral dosage form:** 25 mg.
☐ losartan	**Tablet:** 25 mg; 50 mg; 100 mg
spironolactone	**Tablet:** 25 mg.
Complementary List	
dopamine	***Injection:*** *40 mg/ mL (hydrochloride) in 5- mL vial.*
12.5 Antithrombotic medicines	
12.5.1 Anti-platelet medicines	

12. CARDIOVASCULAR MEDICINES *(continued)*	
acetylsalicylic acid	**Tablet:** 100 mg.
clopidogrel	**Tablet:** 75 mg; 300 mg
12.5.2 Thrombolytic medicines	
Complementary List	
streptokinase	***Powder for injection:*** *1.5 million IU in vial.*
12.6 Lipid-lowering agents	
☐ simvastatin*	**Tablet:** 5 mg; 10 mg; 20 mg; 40 mg. * For use in high-risk patients.
13. DERMATOLOGICAL MEDICINES (topical)	
13.1 Antifungal medicines	
☐ miconazole	**Cream or ointment:** 2% (nitrate).
selenium sulfide	**Detergent-based suspension:** 2%.
sodium thiosulfate	**Solution:** 15%.
terbinafine	**Cream:** 1% or Ointment: 1% terbinafine hydrochloride.
13.2 Anti-infective medicines	
mupirocin	**Cream (as mupirocin calcium):** 2%. **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] >2 months.
13.3 Anti-inflammatory and antipruritic medicines	
☐ betamethasone [a]	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
☐ calamine	**Lotion.**
☐ hydrocortisone	**Cream or ointment:** 1% (acetate).
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	**Cream or lotion:** 5%.
coal tar	**Solution:** 5%.
fluorouracil	**Ointment:** 5%.
☐ podophyllum resin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*	
urea	**Cream or ointment:** 5%; 10%.
13.5 Scabicides and pediculicides	
☐ benzyl benzoate [a]	**Lotion:** 25%. [a] >2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.
14. DIAGNOSTIC AGENTS	
14.1 Ophthalmic medicines	
fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide	**Eye drops:** 0.5%.
14.2 Radiocontrast media	
☐ amidotrizoate	**Injection:** 140 mg to 420 mg iodine (as sodium or meglumine salt)/ mL in 20- mL ampoule.
barium sulfate	**Aqueous suspension.**
☐ iohexol	**Injection:** 140 mg to 350 mg iodine/ mL in 5- mL; 10- mL; 20- mL ampoules.
Complementary List	
barium sulfate [c]	***Aqueous suspension.***
☐*meglumine iotroxate*	***Solution:*** *5 g to 8 g iodine in 100 mL to 250 mL.*
15. DISINFECTANTS AND ANTISEPTICS	
15.1 Antiseptics	
☐ chlorhexidine	**Solution:** 5% (digluconate).
☐ ethanol	**Solution:** 70% (denatured).
☐ povidone iodine	**Solution:** 10% (equivalent to 1% available iodine).
15.2 Disinfectants	
alcohol based hand rub	**Solution:** containing ethanol 80% volume /volume **Solution:** containing isopropyl alcohol 75% volume/volume
☐ chlorine base compound	**Powder:** (0.1% available chlorine) for solution.
☐ chloroxylenol	**Solution:** 4.8%.
glutaral	**Solution:** 2%.

16. DIURETICS

amiloride	**Tablet:** 5 mg (hydrochloride).
☐ furosemide	**Injection:** 10 mg/ mL in 2- mL ampoule. **Oral liquid:** 20 mg/5 mL [c]. **Tablet:** 10 mg [c]; 20 mg [c]; 40 mg.
☐ hydrochlorothiazide	**Solid oral dosage form:** 25 mg.
mannitol	**Injectable solution:** 10%; 20%.
spironolactone	**Tablet:** 25 mg.

Complementary List [c]

☐ *hydrochlorothiazide*	***Tablet (scored):*** *25 mg.*
mannitol	***Injectable solution:*** *10%; 20%.*
spironolactone	***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.* ***Tablet:*** *25 mg.*

17. GASTROINTESTINAL MEDICINES

Complementary List [c]

☐ *pancreatic enzymes*	*Age-appropriate formulations and doses including lipase, protease and amylase.*

17.1 Antiulcer medicines

☐ omeprazole	**Powder for injection:** 40 mg in vial **Powder for oral liquid:** 20 mg; 40 mg sachets. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
☐ ranitidine	**Injection:** 25 mg/ mL (as hydrochloride) in 2- mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt). **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL. **Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide [a]	**Injection:** 5 mg (hydrochloride)/ mL in 2- mL ampoule. **Oral liquid:** 5 mg/5 mL [c]. **Tablet:** 10 mg (hydrochloride). [a] Not in neonates.

17. GASTROINTESTINAL MEDICINES *(continued)*	
ondansetron [a]	**Injection:** 2 mg base/ mL in 2- mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base; Eq 24 mg base. [a] >1 month.
17.3 Anti-inflammatory medicines	
☐ sulfasalazine	**Retention enema.** **Suppository:** 500 mg. **Tablet:** 500 mg.
Complementary List	
☐ *hydrocortisone*	***Retention enema.*** ***Suppository:*** *25 mg (acetate).* *(the ☐ only applies to hydrocortisone retention enema).*
17.4 Laxatives	
☐ senna	**Tablet: 7**.5 mg (sennosides) (or traditional dosage forms).
17.5 Medicines used in diarrhoea	
17.5.1 Oral rehydration	
oral rehydration salts	**Powder for dilution** in 200 mL; 500 mL; 1 L. glucose: 75 mEq sodium: 75 mEq or mmol/L chloride: 65 mEq or mmol/L potassium: 20 mEq or mmol/L citrate: 10 mmol/L osmolarity: 245 mOsm/L glucose: 13.5 g/L sodium chloride: 2.6 g/L potassium chloride: 1.5 g/L trisodium citrate dihydrate*: 2.9 g/L *trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.
17.5.2 Medicines for diarrhoea	
zinc sulfate*	**Solid oral dosage form:** 20 mg. * In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	**Tablet:** 100 micrograms (acetate).
hydrocortisone	**Tablet:** 5 mg; 10 mg; 20 mg.

18.2 Androgens

Complementary List

testosterone	***Injection:*** *200 mg (enanthate) in 1- mL ampoule.*

18.3 Contraceptives

18.3.1 Oral hormonal contraceptives

☐ ethinylestradiol + ☐ levonorgestrel	**Tablet:** 30 micrograms + 150 micrograms.
☐ ethinylestradiol + ☐ norethisterone	**Tablet:** 35 micrograms + 1 mg.
levonorgestrel	**Tablet:** 30 micrograms; 750 micrograms (pack of two); 1.5 mg.
ulipristal	**Tablet:** 30 mg (as acetate)

18.3.2 Injectable hormonal contraceptives

estradiol cypionate + medroxyprogesterone acetate	**Injection:** 5 mg + 25 mg.
medroxyprogesterone acetate	**Injection (intramuscular):** 150 mg/ mL in 1- mL vial. **Injection (subcutaneous):** 104 mg/0.65 mL in pre-filled syringe or single-dose injection delivery system.
norethisterone enantate	**Oily solution:** 200 mg/ mL in 1- mL ampoule.

18.3.3 Intrauterine devices

copper-containing device	
levonorgestrel-releasing intrauterine system	Intrauterine system with reservoir containing 52 mg of levonorestrel

18.3.4 Barrier methods

condoms	
diaphragms	

18.3.5 Implantable contraceptives

etonogestrel-releasing implant	Single-rod etonogestrel-releasing implant, containing 68 mg of etonogestrel.
levonorgestrel-releasing implant	Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total).

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES *(continued)*	
18.3.6 Intravaginal contraceptives	
progesterone vaginal ring*	Progesterone-releasing vaginal ring containing 2.074 g of micronized progesterone. *For use in women actively breastfeeding at least 4 times per day
18.4 Estrogens	
18.5 Insulins and other medicines used for diabetes	
☐ gliclazide*	Solid oral dosage form: (controlled-release tablets) 30 mg; 60 mg; 80 mg. * glibenclamide not suitable above 60 years.
glucagon	**Injection:** 1 mg/ mL.
insulin injection (soluble)	**Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial.
intermediate-acting insulin	**Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial (as compound insulin zinc suspension or isophane insulin).
metformin	**Tablet:** 500 mg (hydrochloride).
Complementary List [c]	
metformin	***Tablet:*** *500 mg (hydrochloride).*
18.6 Ovulation inducers	
Complementary List	
clomifene	***Tablet:*** *50 mg (citrate).*
18.7 Progestogens	
☐ medroxyprogesterone acetate	**Tablet:** 5 mg.
18.8 Thyroid hormones and antithyroid medicines	
levothyroxine	**Tablet:** 25 micrograms [c]; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	**Tablet:** 60 mg.
☐ propylthiouracil	**Tablet:** 50 mg.
Complementary List [c]	
Lugol's solution	***Oral liquid:*** *about 130 mg total iodine/ mL.*
potassium iodide	***Tablet:*** *60 mg.*
propylthiouracil	***Tablet:*** *50 mg.*

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	**Injection.**

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements.

Anti-venom immunoglobulin*	**Injection.** * Exact type to be defined locally.
diphtheria antitoxin	Injection: 10 000 IU; 20 000 IU in vial.

19. IMMUNOLOGICALS *(continued)*

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at 10 February 2017. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at:

http://www.who.int/immunization/documents/positionpapers/en/index.html.

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at:

http://www.who.int/immunization/policy/immunization_tables/en/index.html.

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

Recommendations for all

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

HPV vaccine

measles vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

Recommendations for certain regions

Japanese encephalitis vaccine

yellow fever vaccine

tick-borne encephalitis vaccine

19. IMMUNOLOGICALS *(continued)*

Recommendations for some high-risk populations

cholera vaccine

hepatitis A vaccine

meningococcal meningitis vaccine

rabies vaccine

typhoid vaccine

Recommendations for immunization programmes with certain characteristics

influenza vaccine (seasonal)

mumps vaccine

varicella vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS

☐ atracurium	**Injection:** 10 mg/ mL (besylate).
neostigmine	**Injection:** 500 micrograms in 1- mL ampoule; 2.5 mg (metilsulfate) in 1- mL ampoule.
	Tablet: 15 mg (bromide).
suxamethonium	**Injection:** 50 mg (chloride)/ mL in 2- mL ampoule.
	Powder for injection (chloride), in vial.
☐ vecuronium [C]	**Powder for injection:** 10 mg (bromide) in vial.
Complementary List	
pyridostigmine	***Injection:*** *1 mg in 1- mL ampoule.*
	Tablet: *60 mg (bromide).*
☐ *vecuronium*	***Powder for injection:*** *10 mg (bromide) in vial.*

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% W/W.
azithromycin	**Solution (eye drops):** 1.5%.
erythromycin*	**Ointment:** 0.5% [c] *Infections due to Chlamydia trachomatis or Neisseria gonorrhoea.
☐ gentamicin	**Solution (eye drops):** 0.3% (sulfate).
natamycin	**Suspension:** (eye drops): 5%
☐ ofloxacin	**Solution (eye drops):** 0.3%.
☐ tetracycline	**Eye ointment:** 1% (hydrochloride).

21.2 Anti-inflammatory agents

☐ prednisolone	**Solution (eye drops):** 0.5% (sodium phosphate).

21.3 Local anaesthetics

☐ tetracaine [a]	**Solution (eye drops):** 0.5% (hydrochloride). [a] Not in preterm neonates.

21.4 Miotics and antiglaucoma medicines

acetazolamide	**Tablet:** 250 mg.
latanoprost	**Solution (eye drops):** latanoprost 50 micrograms/mL
☐ pilocarpine	**Solution (eye drops):** 2%; 4% (hydrochloride or nitrate).
☐ timolol	**Solution (eye drops):** 0.25%; 0.5% (as hydrogen maleate).

21.5 Mydriatics

atropine* [a]	**Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate). * [c] Or homatropine (hydrobromide) or cyclopentolate (hydrochloride). [a] >3 months.
Complementary List	
epinephrine (adrenaline)	***Solution (eye drops):** 2% (as hydrochloride).*

21.6 Anti-vascular endothelial growth factor (VEGF) preparations

Complementary List	
bevacizumab	***Injection:** 25 mg/ mL.*

22. OXYTOCICS AND ANTIOXYTOCICS

22.1 Oxytocics

☐ ergometrine	**Injection:** 200 micrograms (hydrogen maleate) in 1- mL ampoule.
misoprostol	**Tablet:** 200 micrograms. - Management of incomplete abortion and miscarriage; - Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used **Vaginal tablet:** 25 micrograms.* * Only for use for induction of labour where appropriate facilities are available.
oxytocin	**Injection:** 10 IU in 1- mL.
Complementary List	
mifepristone – misoprostol**	***Tablet** 200 mg – **tablet** 200 micrograms.* ** Requires close medical supervision.*
Where permitted under national law and where culturally acceptable.	

22.2 Antioxytocics (tocolytics)

nifedipine	**Immediate-release capsule:** 10 mg.

23. PERITONEAL DIALYSIS SOLUTION

Complementary List	
intraperitoneal dialysis solution *(of appropriate composition)*	**Parenteral solution.**

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines used in psychotic disorders

☐ chlorpromazine	**Injection:** 25 mg (hydrochloride)/ mL in 2- mL ampoule. **Oral liquid:** 25 mg (hydrochloride)/5 mL. **Tablet:** 100 mg (hydrochloride).
☐ fluphenazine	**Injection:** 25 mg (decanoate or enantate) in 1- mL ampoule.
☐ haloperidol	**Injection:** 5 mg in 1- mL ampoule. **Tablet:** 2 mg; 5 mg.
risperidone	**Solid oral dosage form:** 0.25 mg to 6.0 mg.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

Complementary List	
chlorpromazine [c]	***Injection:*** *25 mg (hydrochloride)/ mL in 2- mL ampoule.* ***Oral liquid:*** *25 mg (hydrochloride)/5 mL.* ***Tablet:*** *10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).*
clozapine	***Solid oral dosage form:*** *25 to 200 mg.*
haloperidol [c]	***Injection:*** *5 mg in 1- mL ampoule.* ***Oral liquid:*** *2 mg/ mL.* ***Solid oral dosage form:*** *0.5 mg; 2 mg; 5 mg.*

24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders

☐ amitriptyline	**Tablet:** 25 mg; 75mg. (hydrochloride).
fluoxetine	**Solid oral dosage form:** 20 mg (as hydrochloride).
Complementary List [c]	
fluoxetine [a]	***Solid oral dosage form:*** *20 mg (as hydrochloride).* [a] *>8 years.*

24.2.2 Medicines used in bipolar disorders

carbamazepine	**Tablet (scored):** 100 mg; 200 mg.
lithium carbonate	**Solid oral dosage form:** 300 mg.
valproic acid (sodium valproate)	**Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate).

24.3 Medicines for anxiety disorders

☐ diazepam	**Tablet (scored):** 2 mg; 5 mg.

24.4 Medicines used for obsessive compulsive disorders

clomipramine	**Capsule:** 10 mg; 25 mg (hydrochloride).

24.5 Medicines for disorders due to psychoactive substance use

nicotine replacement therapy (NRT)	**Chewing gum:** 2 mg; 4 mg (as polacrilex). Transdermal patch: 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

Complementary List

☐ *methadone**	***Concentrate for oral liquid:*** *5 mg/ mL; 10 mg/ mL (hydrochloride).* ***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL (hydrochloride).* ** The square box is added to include buprenorphine. The medicines should only be used within an established support programme.*

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

☐ beclometasone	**Inhalation (aerosol):** 50 micrograms (dipropionate) per dose; 100 micrograms (dipropionate) per dose (as CFC free forms).
☐ budesonide [C]	**Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose.
☐ budesonide + formoterol	**Dry powder inhaler:** 100 micrograms + 6 micrograms per dose; 200 micrograms + 6 micrograms per dose
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1- mL ampoule.
ipratropium bromide	**Inhalation (aerosol):** 20 micrograms/metered dose.
☐ salbutamol	**Inhalation (aerosol):** 100 micrograms (as sulfate) per dose. **Injection:** 50 micrograms (as sulfate)/ mL in 5- mL ampoule. **Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose. **Respirator solution for use in nebulizers:** 5 mg (as sulfate)/ mL.

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**

26.2 Parenteral

glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES *(continued)*	
glucose with sodium chloride	**Injectable solution:** 4% glucose, 0.18% sodium chloride (equivalent to Na+ 30 mmol/L, Cl- 30 mmol/L). **Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L) [c] .
potassium chloride	**Solution:** 11.2% in 20- mL ampoule (equivalent to K+ 1.5 mmol/ mL, Cl- 1.5 mmol/ mL). **Solution for dilution:** 7.5% (equivalent to K 1 mmol/ mL and Cl 1 mmol/ mL) [c] ; 15% (equivalent to K 2 mmol/ mL and Cl 2 mmol/ mL) [c] .
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+ 167 mmol/L, HCO3- 167 mmol/L). **Solution:** 8.4% in 10- mL ampoule (equivalent to Na+ 1000 mmol/L, HCO3-1000 mmol/L).
☐ sodium lactate, compound solution	**Injectable solution.**
26.3 Miscellaneous	
water for injection	2- mL; 5- mL; 10- mL ampoules.
27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.
calcium	**Tablet:** 500 mg (elemental).
colecalciferol [c]	**Oral liquid:** 400 IU/ mL. **Solid oral dosage form:** 400 IU; 1000 IU. * Ergocalciferol can be used as an alternative.
☐ ergocalciferol	**Oral liquid:** 250 micrograms/ mL (10 000 IU/ mL). **Solid oral dosage form:** 1.25 mg (50 000 IU).
iodine	**Capsule:** 200 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
☐ nicotinamide	**Tablet:** 50 mg.

27. VITAMINS AND MINERALS *(continued)*

pyridoxine	**Tablet:** 25 mg (hydrochloride).
retinol	**Capsule:** 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). **Oral oily solution:** 100 000 IU (as palmitate)/ mL in multidose dispenser. **Tablet (sugar-coated):** 10 000 IU (as palmitate). **Water-miscible injection:** 100 000 IU (as palmitate) in 2- mL ampoule.
riboflavin	**Tablet:** 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	**Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:*** *100 mg/ mL in 10- mL ampoule.*

28. EAR, NOSE AND THROAT MEDICINES [c]

acetic acid	**Topical:** 2%, in alcohol.
☐ budesonide	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin	**Topical:** 0.3% drops (as hydrochloride).
☐ xylometazoline [a]	**Nasal spray:** 0.05%. [a] Not in children less than 3 months.

29. SPECIFIC MEDICINES FOR NEONATAL CARE

29.1 Medicines administered to the neonate [c]

caffeine citrate	**Injection:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL). **Oral liquid:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL).
chlorhexidine	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care) [c].
Complementary List	
☐ *ibuprofen*	***Solution for injection:*** *5 mg/ mL.*
☐ *prostaglandin E*	***Solution for injection:*** ***Prostaglandin E1:*** *0.5 mg/ mL in alcohol.*

29. SPECIFIC MEDICINES FOR NEONATAL CARE *(continued)*	
	Prostaglandin E 2: *1 mg/ mL.*
surfactant	***Suspension for intratracheal instillation:*** *25 mg/ mL or 80 mg/ mL.*
29.2 Medicines administered to the mother	
dexamethasone	**Injection:** 4 mg/ mL dexamethasone phosphate (as disodium salt)
30. MEDICINES FOR DISEASES OF JOINTS	
30.1 Medicines used to treat gout	
allopurinol	**Tablet:** 100 mg.
30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)	
chloroquine	T**ablet:** 100 mg; 150 mg (as phosphate or sulfate).
Complementary List	
azathioprine	***Tablet:*** *50 mg.*
hydroxychloroquine cd	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium salt).*
penicillamine	***Solid oral dosage form:*** *250 mg.*
sulfasalazine	**Tablet:** *500 mg.*
30.3 Juvenile joint diseases	
acetylsalicylic acid* (acute or chronic use)	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg. * For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

Table 1.1: Medicines with age or weight restrictions

artesunate + pyronaridine tetraphosphate	> 5 kg
atazanavir	>25 kg
atropine	>3 months
benzyl benzoate	>2 years
betamethasone topical preparations	hydrocortisone preferred in neonates
cefazolin	>1 month
ceftriaxone	>41 weeks corrected gestational age
darunavir	> 3 years
delamanid	> 6 years
dihydroartemisinin + piperaquine phosphate	> 5 kg
diloxanide	>25 kg
doxycycline	>8 years (except for serious infections e.g. cholera)
efavirenz	>3 years or >10 kg
fluoxetine	>8 years
ibuprofen	>3 months (except IV form for patent ductus arteriosus)
mefloquine	>5 kg or >3 months
metoclopramide	Not in neonates
nevirapine	> 6 weeks
ondansetron	>1 month
silver sulfadiazine	>2 months
tetracaine	Not in preterm neonates
trimethoprim	>6 months
xylometazoline	>3 months

Table 1.2: Explanation of dosage forms

A. Principal dosage forms used in EML – oral administration

Term	Definition
Solid oral dosage form	Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability. The term 'solid oral dosage form' is never intended to allow any type of modified-release tablet.
Tablets	Refers to: • uncoated or coated (film-coated or sugar-coated) • tablets that are intended to be swallowed whole; • unscored and scored*; • tablets that are intended to be chewed before being swallowed; • tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed; • tablets that are intended to be crushed before being swallowed. The term 'tablet' without qualification is never intended to allow any type of modified-release tablet.
Tablets (qualified)	Refers to a specific type of tablet: **chewable** - tablets that are intended to be chewed before being swallowed; **dispersible** - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed; **soluble** - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed; **crushable** - tablets that are intended to be crushed before being swallowed; **scored** - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet;

	sublingual - tablets that are intended to be placed beneath the tongue. The term 'tablet' is always qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release), prolonged-release or another modified-release form.
Capsules	Refers to hard or soft capsules. The term 'capsule' without qualification is never intended to allow any type of modified-release capsule.
Capsules (qualified)	The term 'capsule' with qualification refers to **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Granules	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid. The term 'granules' without further qualification is never intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be swallowed i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but not those preparations intended for oromucosal administration e.g. gargles and mouthwashes. Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

B. Principal dosage forms used in EML – parenteral administration

Term	Definition
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term `injection' is qualified by `(oily)' in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, pressurized inhalation, nebulizer.

Annex 2

WHO Model List of Essential Medicines for Children (March 2017)

Explanatory notes

This Model List is intended for use for children up to 12 years of age.

The core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **Complementary** List presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost–effectiveness in a variety of settings.

The **square box symbol** (□) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.

Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The format and numbering of the 20th WHO Model List of Essential Medicines have been retained but, as indicated in the text, some sections have been deleted because they contain medicines that are not relevant for children.

a indicates that there is an age or weight restriction on use of the medicines; the details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/.

Medicines and dosage forms are listed in alphabetical order within each section and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of The International Pharmacopoeia http://www.who.int/medicines/publications/pharmacopoeia.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 Inhalational medicines

halothane	**Inhalation.**
isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medical gas).

1.1.2 Injectable medicines

ketamine	**Injection:** 50 mg (as hydrochloride)/mL in 10-mL vial.
propofol *	**Injection:** 10 mg/mL; 20 mg/mL. * Thiopental may be used as an alternative depending on local availability and cost.

1.2 Local anaesthetics

☐ bupivacaine	**Injection:** 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4-mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2-mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.

1.3 Preoperative medication and sedation for short-term procedures

atropine	**Injection:** 1 mg (sulfate) in 1-mL ampoule.
☐ midazolam	**Injection:** 1 mg/mL. **Oral liquid:** 2 mg/mL. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection:** 10 mg (sulfate or hydrochloride) in 1-mL ampoule.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*

1.4 Medical gases

oxygen*	**Inhalation** For use in the management of hypoxaemia. *No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE

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

ibuprofen [a]	**Oral liquid:** 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol*	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Suppository:** 100 mg. **Tablet:** 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2.2 Opioid analgesics

☐ morphine*	**Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1-mL ampoule. **Oral liquid:** 10 mg (morphine hydrochloride or morphine sulfate)/5 mL. **Tablet (slow release):** 10 mg – 200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate). *Alternatives limited to hydromorphone and oxycodone.
Complementary List	
*methadone**	***Tablet:** 5 mg; 10 mg (as hydrochloride).* ***Oral liquid:** 5mg/ 5mL; 10mg/ 5mL (as hydrochloride).* ***Concentrate for oral liquid:** 5 mg/ mL; 10mg/ mL (as hydrochloride)* **For the management of cancer pain.*

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*

2.3 Medicines for other symptoms common in palliative care

amitriptyline	**Tablet:** 10 mg; 25 mg.
cyclizine	**Injection:** 50 mg/mL. **Tablet:** 50 mg.
dexamethasone	**Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt). **Oral liquid:** 2 mg/5 mL. **Tablet:** 2 mg.
diazepam	**Injection:** 5 mg/mL. **Oral liquid:** 2 mg/5 mL. **Rectal solution:** 2.5 mg; 5 mg; 10 mg. **Tablet:** 5 mg; 10 mg.
docusate sodium	**Capsule:** 100 mg. **Oral liquid:** 50 mg/5 mL.
fluoxetine [a]	**Solid oral dosage form:** 20 mg (as hydrochloride). [a] >8 years.
hyoscine hydrobromide	**Injection:** 400 micrograms/mL; 600 micrograms/mL. **Transdermal patches:** 1 mg/72 hours.
lactulose	**Oral liquid:** 3.1–3.7 g/5 mL.
midazolam	**Injection:** 1 mg/mL; 5 mg/mL. **Oral liquid:** 2mg/mL. **Solid oral dosage form:** 7.5 mg; 15 mg.
ondansetron [a]	**Injection:** 2 mg base/mL in 2-mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] >1 month.
senna	**Oral liquid:** 7.5 mg/5 mL.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

dexamethasone	**Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt).
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1-mL ampoule.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS *(continued)*	
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.
☐ loratadine *	**Oral liquid:** 1 mg/mL. **Tablet:** 10 mg. *There may be a role for sedating antihistamines for limited indications.
☐ prednisolone	**Oral liquid:** 5 mg/mL. **Tablet:** 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Powder.**
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/mL in 10-mL ampoule. Oral liquid: 10%; 20%.
atropine	**Injection:** 1 mg (sulfate) in 1-mL ampoule.
calcium gluconate	**Injection:** 100 mg/mL in 10-mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1-mL ampoule.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:*** *50 mg/mL in 2-mL ampoule.*
fomepizole	***Injection:*** *5 mg/mL (sulfate) in 20-mL ampoule or 1 g/mL (base) in* *1.5-mL ampoule.*
sodium calcium edetate	***Injection:*** *200 mg/mL in 5-mL ampoule.*
succimer	***Solid oral dosage form:*** *100 mg.*

5. ANTICONVULSANTS/ANTIEPILEPTICS	
carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg.
diazepam	**Gel or rectal solution:** 5 mg/mL in 0.5 mL; 2-mL; 4-mL tubes.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. *as adjunctive therapy for treatment-resistant partial or generalized seizures.
☐ lorazepam	**Parenteral formulation:** 2 mg/mL in 1-mL ampoule; 4 mg/mL in 1-mL ampoule.
midazolam	**Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL **Ampoule*:** 1 mg/ mL; 10 mg/mL *for buccal administration when solution for oromucosal administration is not available
phenobarbital	**Injection:** 200 mg/mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/mL in 5-mL vial (sodium salt). **Oral liquid:** 25 mg to 30 mg/5 mL.* **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium salt). **Tablet (chewable):** 50 mg. * The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
valproic acid (sodium valproate)	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate).
Complementary List	
ethosuximide	***Capsule:** 250 mg.* ***Oral liquid:** 250 mg/5 mL.*
valproic acid (sodium valproate)	***Injection:** 100 mg/ mL in 4- mL ampoule; 100 mg/ mL in 10- mL ampoule.*

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

albendazole	**Tablet (chewable):** 400 mg.
ivermectin	**Tablet (scored):** 3 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 600 mg.
pyrantel	**Oral liquid:** 50 mg (as embonate **or** pamoate)/mL. **Tablet (chewable):** 250 mg (as embonate **or** pamoate).

6.1.2 Antifilarials

albendazole	**Tablet (chewable):** 400 mg.
diethylcarbamazine	**Tablet: 50 mg;** 100 mg (dihydrogen citrate).
ivermectin	**Tablet (scored):** 3 mg.

6.1.3 Antischistosomals and other antitrematode medicines

praziquantel	**Tablet:** 600 mg.
triclabendazole	**Tablet:** 250 mg.

Complementary List

*oxamniquine**	**Capsule:** *250 mg.* **Oral liquid:** *250 mg/5 mL.* ** Oxamniquine is listed for use when praziquantel treatment fails.*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, three different categories were developed – ACCESS, WATCH and RESERVE groups.

Group 1 - KEY ACCESS ANTIBIOTICS

To improve both access and clinical outcomes antibiotics that were first or second choice antibiotics in at least one of the reviewed syndromes are designated as key ACCESS antibiotics, emphasizing their role as the antibiotics that should be widely available, affordable and quality-assured. ACCESS antibiotics are listed below. Selected ACCESS antibiotics may also be included in the WATCH group.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.1 Beta-lactam medicines		***6.2.2 Other antibacterials***	
amoxicillin	cefotaxime*	amikacin	gentamicin
amoxicillin + clavulanic acid	ceftriaxone*	azithromycin*	metronidazole
ampicillin	cloxacillin	chloramphenicol	nitrofurantoin
benzathine benzylpenicillin	phenoxymethylpenicillin	ciprofloxacin*	spectinomycin (EML only)
benzylpenicillin	piperacillin + tazobactam*	clarithromycin*	sulfamethoxazole + trimethoprim
cefalexin	procaine benzyl penicillin	clindamycin	vancomycin (oral)*
cefazolin	*meropenem**	doxycycline	*vancomycin (parenteral)**
cefixime*			

Italics = Complementary List

*Watch group antibiotics included in the EML/EMLc only for specific, limited indications

The 2017 Expert Committee identified the following antibiotics or antibiotic classes that should be the subject of a specific stewardship focus. Antibiotics or antibiotic classes in these groups are designated accordingly in the EML/EMLc. The “WATCH” and “RESERVE” stewardship groups could assist in activities such as local, national and global monitoring of use; development of guidelines and educational activities.

Group 2 - WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and so are recommended as first or second choice treatments only for a specific, limited number of indications. These medicines should be prioritized as key targets of stewardship programs and monitoring.

This group includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine[1] and/or antibiotics that are at relatively high risk of selection of bacterial resistance.

6. ANTI-INFECTIVE MEDICINES *(continued)*
Watch group antibiotics
Quinolones and fluoroquinolones e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
3rd-generation cephalosporins (with or without beta-lactamase inhibitor) e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime
Macrolides e.g. azithromycin, clarithromycin, erythromycin
Glycopeptides e.g. teicoplanin, vancomycin
Antipseudomonal penicillins + beta-lactamase inhibitor e.g. piperacillin-tazobactam
Carbapenems e.g. meropenem, imipenem + cilastatin
Penems e.g. faropenem

6. ANTI-INFECTIVE MEDICINES *(continued)*

Group 3 - RESERVE GROUP ANTIBIOTICS

This group includes antibiotics that should be treated as "last resort" options that should be accessible, but whose use should be tailored to highly specific patients and settings, when all alternatives have failed (e.g., serious, life-threatening infections due to multi-drug resistant bacteria). These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

Reserve group antibiotics	
Aztreonam	Fosfomycin (IV)
4th generation cephalosporins e.g. cefepime	Oxazolidinones e.g. linezolid
5th generation cephalosporins e.g. ceftaroline	Tigecycline
Polymyxins e.g. polymyxin B, colistin	Daptomycin

6.2.1 Beta-lactam medicines

amoxicillin	**Powder for oral liquid:** 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL. **Solid oral dosage form:** 250 mg; 500 mg (as trihydrate). **Powder for injection:** 250 mg; 500 mg; 1 g (as sodium) in vial.	
amoxicillin	**FIRST CHOICE** *- community acquired pneumonia (mild to moderate)* *- community acquired pneumonia (severe)* *- complicated severe acute malnutrition* - exacerbations of COPD *- lower urinary tract infections* *- otitis media* *- pharyngitis* *- sepsis in neonates and children* *- sinusitis* *- uncomplicated severe acute malnutrition*	**SECOND CHOICE** *- acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

amoxicillin + clavulanic acid	**Oral liquid:** 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL. **Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt). **Powder for injection:** 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.	
	FIRST CHOICE *- community acquired pneumonia (severe)* *- complicated intraabdominal infections (mild to moderate)* *- hospital acquired pneumonia* *- low-risk febrile neutropenia* *- lower urinary tract infections* *- sinusitis* *- skin and soft tissue infections*	**SECOND CHOICE** *- bone and joint infections* *- community-acquired pneumonia (mild to moderate)* *- community acquired pneumonia (severe)* *- otitis media*
ampicillin	**Powder for injection:** 500 mg; 1 g (as sodium salt) in vial.	
	FIRST CHOICE *- community acquired pneumonia (severe)* *- complicated severe acute malnutrition* *- sepsis in neonates and children*	**SECOND CHOICE** *- acute bacterial meningitis*
benzathine benzylpenicillin	**Powder for injection:** 900 mg benzylpenicillin (= 1.2 million IU) in 5- mL vial; 1.44 g benzylpenicillin (= 2.4 million IU) in 5- mL vial.	
	FIRST CHOICE *- syphilis (congenital)*	**SECOND CHOICE**

6. ANTI-INFECTIVE MEDICINES *(continued)*

benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium **or** potassium salt) in vial.	
	FIRST CHOICE *-community acquired pneumonia (severe)* *- complicated severe acute malnutrition* *- sepsis in neonates and children* *- syphilis (congenital)*	**SECOND CHOICE** *- acute bacterial meningitis*
cefalexin	**Powder for reconstitution with water:** 125 mg/5 mL; 250 mg/5 mL (anhydrous). **Solid oral dosage form:** 250 mg (as monohydrate).	
	FIRST CHOICE	**SECOND CHOICE** *- pharyngitis* *- skin and soft tissue infections*
cefazolin* [a]	**Powder for injection:** 1 g (as sodium salt) in vial. * also indicated for surgical prophylaxis. [a] >1 month.	
	FIRST CHOICE	**SECOND CHOICE** *- bone and joint infections*
cefixime WATCH GROUP	**Capsule or tablet:** 200 mg; 400 mg (as trihydrate). **Powder for oral liquid:** 100 mg /5 mL	
	FIRST CHOICE	**SECOND CHOICE** *- acute invasive bacterial diarrhoea / dysentery*

6. ANTI-INFECTIVE MEDICINES *(continued)*

cefotaxime*
WATCH GROUP

Powder for injection: 250 mg per vial (as sodium salt)

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
- acute bacterial meningitis	*- bone and joint infections*
-community acquired pneumonia (severe)	*-pyelonephritis or prostatitis (mild to moderate)*
- complicated intraabdominal infections (mild to moderate)	*- sepsis in neonates and children*
- complicated intrabdominal infections (severe)	
- hospital acquired pneumonia	
-pyelonephritis or prostatitis (severe)	

ceftriaxone* [a]
WATCH GROUP

Powder for injection: 250 mg; 1 g (as sodium salt) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] >41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
- acute bacterial meningitis	*- acute invasive bacterial diarrhoea / dysentery*
-community acquired pneumonia (severe)	*- bone and joint infections*
- complicated intraabdominal infections (mild to moderate)	*- pyelonephritis or prostatitis (mild to moderate)*
- complicated intrabdominal infections (severe)	*- sepsis in neonates and children*
- hospital acquired pneumonia	
-pyelonephritis or prostatitis (severe)	

6. ANTI-INFECTIVE MEDICINES *(continued)*

☐ cloxacillin*

Capsule: 500 mg; 1 g (as sodium salt).

Powder for injection: 500 mg (as sodium salt) in vial.

Powder for oral liquid: 125 mg (as sodium salt)/5 mL.

*cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
- bone and joint infections *- skin and soft tissue infections*	*- sepsis in neonates and children*

phenoxymethylpenicillin

Powder for oral liquid: 250 mg (as potassium salt)/5 mL.

Tablet: 250 mg (as potassium salt).

FIRST CHOICE	SECOND CHOICE
- community acquired pneumonia (mild to moderate) *- pharyngitis*	

piperacillin + tazobactam
WATCH GROUP

Powder for injection: 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as sodium salt) + 500 mg (as sodium salt) in vial

FIRST CHOICE	SECOND CHOICE
- complicated intraabdominal infections (severe) *-high-risk febrile neutropenia* *-hospital acquired pneumonia*	

procaine benzylpenicillin*

Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial.

* Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.

FIRST CHOICE	SECOND CHOICE
- syphilis (congenital)	

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

ceftazidime
WATCH GROUP

Powder for injection: *250 mg* **or** *1 g (as pentahydrate) in vial.*

*meropenem** [a]
WATCH GROUP

Powder for injection: *500 mg (as trihydrate); 1 g (as trihydrate) in vial*

[a] *>3 months.*

**imipenem + cilastatin is an alternative except for acute bacterial meningitis where meropenem is preferred.*

FIRST CHOICE	SECOND CHOICE
	- acute bacterial meningitis in neonates *- complicated intraabdominal infections (severe)* *- high-risk febrile neutropenia*

Complementary List – RESERVE GROUP

aztreonam

Powder for injection: *1 g; 2 g in vial*

fifth generation cephalosporins
(with or without beta-lactamase inhibitor)
e.g, ceftaroline

Powder for injection*: 400 mg; 600 mg (as fosamil) in vial*

fourth generation cephalosporins
(with or without beta-lactamase inhibitor)
e.g. cefepime

Powder for injection: *500 mg; 1g; 2g (as hydrochloride) in vial*

6.2.2 Other antibacterials

amikacin

Injection: 250 mg (as sulfate)/mL in 2- mL vial

FIRST CHOICE	SECOND CHOICE
- pyelonephritis or prostatitis (severe)	*- high-risk febrile neutropenia* *- sepsis in neonates and children*

azithromycin*
WATCH GROUP

Capsule: 250 mg; 500 mg (anhydrous).
Oral liquid: 200 mg/5 mL.
* also listed for single-dose treatment of trachoma and yaws.

FIRST CHOICE	SECOND CHOICE
- cholera	*- acute invasive bacterial diarrhoea / dysentery*

6. ANTI-INFECTIVE MEDICINES *(continued)*

chloramphenicol	**Capsule:** *250 mg.* **Oily suspension for injection***: 0.5 g (as sodium succinate)/ mL in 2- mL ampoule. * Only for the presumptive treatment of epidemic meningitis in children older than 2 years. **Oral liquid:** 150 mg (as palmitate)/5 mL. **Powder for injection:** 1 g (sodium succinate) in vial.	
	FIRST CHOICE	**SECOND CHOICE** *- acute bacterial meningitis*
ciprofloxacin WATCH GROUP	**Oral liquid:** 250 mg/5 mL (anhydrous). **Solution for IV infusion:** 2 mg/ mL (as hyclate). **Tablet:** 250 mg (as hydrochloride).	
	FIRST CHOICE *- acute invasive bacterial diarrhoea / dysentery* *- low-risk febrile neutropenia* *- pyelonephritis or prostatitis (mild to moderate)*	**SECOND CHOICE** *- cholera* *- complicated intraabdominal infections (mild to moderate)*
clarithromycin* WATCH GROUP	**Solid oral dosage form:** 500 mg. **Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL **Powder for injection:** 500 mg in vial *erythromycin may be an alternative.	
	FIRST CHOICE	**SECOND CHOICE** *- pharyngitis*
clindamycin	**Capsule:** 150 mg (as hydrochloride). **Injection:** 150 mg (as phosphate)/ mL. **Oral liquid:** 75 mg/5 mL (as palmitate)	
	FIRST CHOICE	**SECOND CHOICE** *- bone and joint infections*
doxycycline [a]	**Oral liquid:** 25 mg/5 mL; 50 mg/5 mL (anhydrous). **Solid oral dosage form:** 50 mg; 100 mg (as hyclate). **Powder for injection:** 100 mg in vial [a] Use in children <8 years only for life-threatening infections when no alternative exists.	
	FIRST CHOICE	**SECOND CHOICE** *- cholera* *-community acquired pneumonia (mild to moderate)*

6. ANTI-INFECTIVE MEDICINES *(continued)*		
gentamicin	**Injection:** 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial.	
	FIRST CHOICE *- community acquired pneumonia (severe)* *- complicated severe acute malnutrition* *- sepsis in neonates and children*	**SECOND CHOICE**
metronidazole	**Injection:** 500 mg in 100- mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Tablet:** 200 mg to 500 mg.	
	FIRST CHOICE *- C. difficile infection* *- complicated intraabdominal infections (mild to moderate)* *- complicated intrabdominal infections (severe)*	**SECOND CHOICE** *- complicated intraabdominal infections (mild to moderate)*
nitrofurantoin	**Oral liquid:** 25 mg/5 mL. **Tablet:** 100 mg.	
	FIRST CHOICE *- lower urinary tract infections*	**SECOND CHOICE**
sulfamethoxazole + trimethoprim*	**Injection:** 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg; *single agent trimethoprim may be an alternative for lower urinary tract infection.	
	FIRST CHOICE *- lower urinary tract infections*	**SECOND CHOICE** *- acute invasive diarrhoea / bacterial dysentery*

6. ANTI-INFECTIVE MEDICINES *(continued)*

vancomycin	**Capsule:** 125 mg; 250 mg (as hydrochloride).	
WATCH GROUP		**SECOND CHOICE** *- C. difficile infection*
Complementary List		
vancomycin	***Powder for injection:*** 250 mg (as hydrochloride) in vial.	
WATCH GROUP	**FIRST CHOICE**	**SECOND CHOICE** *-high-risk febrile neutropenia*
Complementary List – RESERVE GROUP		
daptomycin	***Powder for injection:*** *350 mg; 500 mg in vial*	
fosfomycin	***Powder for injection:*** *2 g; 4 g (as sodium) in vial*	
oxazolindinones *e.g., linezolid*	***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *400 mg; 600 mg.*	
polymyxins *e.g., colistin*	***Powder for injection:*** *1 million I.U. (as colistemethate sodium) in vial*	
tigecycline	***Powder for injection:*** *50 mg in vial*	

6.2.3 Antileprosy medicines

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Capsule:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Solid oral dosage form:** 150 mg; 300 mg.

6.2.4 Antituberculosis medicines

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	**Oral liquid:** 25 mg/ mL. **Tablet:** 100 mg to 400 mg (hydrochloride).

6. ANTI-INFECTIVE MEDICINES *(continued)*

isoniazid	**Oral liquid:** 50 mg/5 mL. **Tablet:** 100 mg to 300 mg. **Tablet (scored):** 50 mg.
isoniazid + pyrazinamide + rifampicin	**Tablet (dispersible):** 50 mg + 150 mg + 75 mg.
isoniazid + rifampicin	**Tablet (dispersible)**: 50 mg + 75 mg.
pyrazinamide	**Oral liquid:** 30 mg/ mL **Tablet:** 400 mg. **Tablet (dispersible):** 150 mg. **Tablet (scored):** 150 mg.
rifampicin	**Oral liquid:** 20 mg/ mL. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine*	**Tablet:** 150 mg *For treatment of latent TB infection (LTBI) only

Complementary List

Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin	***Powder for injection:*** *100 mg; 500 mg; 1 g (as sulfate) in vial.*
capreomycin	***Powder for injection:*** *1 g (as sulfate) in vial.*
clofazimine	***Capsule:*** *50 mg; 100 mg.*
*cycloserine**	***Solid oral dosage form:*** *250 mg.*
delamanid [a]	***Tablet:*** *50 mg.* [a] >6 years
*ethionamide**	***Tablet:*** *125 mg; 250 mg.* **Protionamide may be an alternative.*
kanamycin	***Powder for injection:*** *1 g (as sulfate) in vial.*
levofloxacin	***Tablet:*** *250mg; 500 mg.*
linezolid	***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *400 mg; 600 mg.*
moxifloxacin	***Tablet:*** *400 mg.*
p-aminosalicylic acid	***Granules:*** *4 g in sachet.* ***Tablet:*** *500 mg.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

streptomycin	***Powder for injection:*** 1 g (as sulfate) in vial.

6.3 Antifungal medicines

amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate **or** liposomal complex).
fluconazole	**Capsule:** 50 mg. **Injection:** 2 mg/ mL in vial. **Oral liquid:** 50 mg/5 mL.
flucytosine	**Capsule:** 250 mg. **Infusion:** 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL. **Solid oral dosage form:** 125 mg; 250 mg.
itraconazole*	**Capsule:** 100 mg. **Oral liquid:** 10 mg/mL. *For treatment of chronic pulmonary aspergillosis, acute invasive aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 50 mg/5 mL; 100 000 IU/ mL. **Tablet:** 100 000 IU; 500 000 IU.
voriconazole*	**Tablet:** 50 mg; 200 mg **Powder for injection:** 200 mg in vial **Powder for oral liquid:** 40 mg/mL *For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.

Complementary List

potassium iodide	***Saturated solution.***

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4 Antiviral medicines

6.4.1 Antiherpes medicines

aciclovir	**Oral liquid:** 200 mg/5 mL **Powder for injection:** 250 mg (as sodium salt) in vial. **Tablet:** 200 mg.

6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following three classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

abacavir (ABC)	**Tablet (dispersible, scored):** 60 mg (as sulfate)
lamivudine (3TC)	**Oral liquid:** 50 mg/5 mL. **Tablet:** 150 mg.
zidovudine (ZDV or AZT)	**Oral liquid:** 50 mg/5 mL. **Tablet (dispersible, scored):** 60 mg

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ) [a]	**Tablet:** 200 mg (scored). [a] >3 years or >10 kg.
nevirapine (NVP) [a]	**Oral liquid:** 50 mg/5 mL. **Tablet:** 50 mg (dispersible). [a] > 6 weeks

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir [a]	**Solid oral dosage form:** 100 mg; (as sulfate). [a] >25 kg.
darunavir [a]	**Tablet:** 75 mg; [a] >3 years
lopinavir + ritonavir (LPV/r)	**Oral liquid:** 400 mg + 100 mg/5 mL. **Tablet (heat stable):** 100 mg + 25 mg. **Capsule containing oral pellets:** 40 mg + 10 mg.
ritonavir	**Oral liquid:** 400 mg/5 mL. **Tablet (heat stable):** 25 mg; 100 mg.

6.4.2.4 Integrase inhibitors

raltegravir*	**Tablet (chewable):** 25 mg; 100 mg. **Tablet:** 400 mg *for use in pregnant women and in second-line regimens in accordance with WHO treatement guidelines.

FIXED-DOSE COMBINATIONS

abacavir + lamivudine	**Tablet (dispersible, scored):** 60 mg (as sulfate) + 30 mg; 120 mg (as sulfate) + 60 mg.
lamivudine + nevirapine + zidovudine	**Tablet:** 30 mg + 50 mg + 60 mg.
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg.

6.4.2.5 Medicines for prevention of HIV-related opportunistic infections

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg

6.4.3 Other antivirals

ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10- mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of viral haemorrhagic fevers only.

6. ANTI-INFECTIVE MEDICINES *(continued)*

valganciclovir*	**Powder for oral solution:** 50 mg/mL **Tablet:** 450 mg *For the treatment of cytomegalovirus retinitis (CMVr).
Complementary List	
*oseltamivir**	***Capsule:** 30 mg; 45 mg; 75 mg (as phosphate).* ***Oral powder:** 12 mg/ mL.* ** severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients*

6.4.4 Antihepatitis medicines

6.4.4.1 Medicines for hepatitis B

6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

entecavir	**Oral liquid:** 0.05 mg/ mL **Tablet:** 0.5 mg; 1 mg

~~*6.4.4.2 Medicines for hepatitis C*~~

6.5 Antiprotozoal medicines

6.5.1 Antiamoebic and antigiardiasis medicines

diloxanide [a]	**Tablet:** 500 mg (furoate). [a] >25 kg.
☐ metronidazole	**Injection:** 500 mg in 100- mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Tablet:** 200 mg to 500 mg.

6.5.2 Antileishmaniasis medicines

amphotericin B	**Powder for injection:** 50 mg in vial. As sodium deoxycholate or liposomal complex.
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as the sulfate).
sodium stibogluconate or meglumine antimoniate	**Injection:** 100 mg/ mL, 1 vial = 30 mL or 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5- mL ampoule.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.3 Antimalarial medicines

6.5.3.1 For curative treatment

Medicines for the treatment of P. falciparum malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

amodiaquine*	**Tablet:** 153 mg **or** 200 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
artemether*	**Oily injection:** 80 mg/ mL in 1- mL ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Rectal dosage form:** 50 mg; 100 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care). **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine **or** sulfadoxine + pyrimethamine.
artesunate + amodiaquine*	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. * Other combinations that deliver the target doses required such as 153 mg **or** 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
artesunate + pyronaridine tetraphosphate [a]	**Tablet:** 60 mg + 180 mg **Granules:** 20 mg + 60 mg. [a] > 5 kg
chloroquine*	**Oral liquid:** 50 mg (as phosphate or sulfate)/5 mL. **Tablet:** 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of *P.vivax* infection.
dihydroartemisinin + piperaquine phosphate [a]	**Tablet:** 20 mg + 160 mg; 40 mg + 320 mg [a] > 5 kg

6. ANTI-INFECTIVE MEDICINES *(continued)*	
doxycycline*	**Capsule:** 100 mg (as hydrochloride **or** hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *P.vivax* and *P.ovale* infections, given for 14 days.
quinine*	**Injection:** 300 mg quinine hydrochloride/ mL in 2- mL ampoule. **Tablet:** 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	**Tablet:** 500 mg + 25 mg. * Only in combination with artesunate 50 mg.
6.5.3.2 For prophylaxis	
chloroquine*	**Oral liquid:** 50 mg (as phosphate or sulfate)/5 mL. **Tablet:** 150 mg (as phosphate or sulfate). * For use only in central American regions, for *P.vivax* infections.
doxycycline [a]	**Solid oral dosage form:** 100 mg (as hydrochloride or hyclate). [a] >8 years.
mefloquine [a]	**Tablet:** 250 mg (as hydrochloride). [a] >5 kg **or** >3 months.
proguanil*	**Tablet:** 100 mg (as hydrochloride). * For use only in combination with chloroquine.
6.5.4 Antipneumocystosis and antitoxoplasmosis medicines	
pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine*	**Powder for injection:** 200 mg (as isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	**Powder for injection:** 1 g in vial. * To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg (hydrochloride)/ mL in 100- mL bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
nifurtimox*	**Tablet:** 120 mg. * Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

Complementary List

melarsoprol	***Injection:** 3.6% solution in 5- mL ampoule (180 mg of active compound).*

6.5.5.2 American trypanosomiasis

benznidazole	**Tablet:** 12.5 mg; 100 mg. **Tablet (scored):** 50 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg; 250 mg.

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

ibuprofen	**Tablet:** 200 mg; 400 mg.
paracetamol	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Tablet:** 300 mg to 500 mg.

7.2 For prophylaxis

☐ propranolol	**Tablet:** 20 mg; 40 mg (hydrochloride).

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES

8.1 Immunosuppressive medicines

Complementary List

azathioprine	***Powder for injection:*** *100 mg (as sodium salt) in vial.* ***Tablet (scored):*** *50 mg.*
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/ mL in 1- mL ampoule for organ transplantation.*

8.2 Cytotoxic and adjuvant medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

Complementary List

allopurinol	***Tablet:*** *100 mg; 300 mg.*
asparaginase	***Powder for injection:*** *10 000 IU in vial.* *- Acute lymphoblastic leukaemia.*
bleomycin	***Powder for injection:*** *15 mg (as sulfate) in vial.* *- Hodgkin lymphoma* *- Testicular germ cell tumours* *- Ovarian germ cell tumours*
calcium folinate	***Injection:*** *3 mg/ mL in 10- mL ampoule.* ***Tablet:*** *15 mg.* *- Osteosarcoma* *- Burkitt lymphoma*
carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* *- Osteosarcoma* *- Retinoblastoma*
cisplatin	*Injection: 50 mg/50 mL; 100 mg/100 mL.* *- Osteosarcoma* *- Testicular germ cell tumours* *- Ovarian germ cell tumours*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
cyclophosphamide	***Powder for injection:*** *500 mg in vial.* ***Tablet:*** *25 mg.* - *Rhabdomyosarcoma* - *Ewing sarcoma* - *Acute lymphoblastic leukaemia* - *Burkitt lymphoma* - *Hodgkin lymphoma*
cytarabine	***Powder for injection:*** *100 mg in vial.* - *Acute lymphoblastic leukaemia* - Burkitt lymphoma.
dacarbazine	***Powder for injection:*** *100 mg in vial.* - *Hodgkin lymphoma*
dactinomycin	***Powder for injection:*** *500 micrograms in vial.* - *Rhabdomyosarcoma* - *Wilms tumour*
daunorubicin	***Powder for injection:*** *50 mg (hydrochloride) in vial.* - *Acute lymphoblastic leukaemia*
doxorubicin	***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* - *Osteosarcoma* - *Ewing sarcoma* - *Acute lymphoblastic leukaemia* - *Wilms tumour* - *Burkitt lymphoma* - *Hodgkin lymphoma*
etoposide	***Capsule:*** *100 mg.* ***Injection:*** 20 mg/ mL in 5- mL ampoule. - Retinoblastoma - Ewing sarcoma - Acute lymphoblastic leukaemia - Burkitt lymphoma - Hodgkin lymphoma - Testicular germ cell tumours - Ovarian germ cell tumours

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*

filgrastim	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe 300 micrograms/mL in 1- mL vial, 480 mg/1.6 mL in 1.6- mL vial.* *- Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.* *- Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* *- To facilitate administration of dose dense chemotherapy regimens*
ifosfamide	***Powder for injection:*** *500 mg vial; 1-g vial; 2-g vial.* *- Osteosarcoma* *- Rhabdomyosarcoma* *- Ewing sarcoma* *- Testicular germ cell tumour* *- Ovarian germ cell tumour*
mercaptopurine	***Tablet:*** *50 mg.* *- Acute lymphoblastic leukaemia*
mesna	***Injection:*** *100 mg/ mL in 4- mL and 10- mL ampoules.* ***Tablet:*** *400 mg; 600 mg.* *- Osteosarcoma* *- Rhabdomyosarcoma* *- Ewing sarcoma.* *- Testicular germ cell tumour* *- Ovarian germ cell tumour*
methotrexate	***Powder for injection:*** *50 mg (as sodium salt) in vial.* ***Tablet:*** *2.5 mg (as sodium salt).* *- Osteosarcoma* *- Acute lymphoblastic leukaemia*
paclitaxel	***Powder for injection:*** *6 mg/ mL.* *- Ovarian germ cell tumour*
tioguanine	***Solid oral dosage form:*** *40 mg.* *- Acute lymphoblastic leukaemia.*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*

vinblastine	***Powder for injection:*** *10 mg (sulfate) in vial.* - *Testicular germ cell tumour* - *Ovarian germ cell tumour* - *Hodgkin lymphoma*
vincristine	***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* - *Retinoblastoma* - *Rhabdomyosarcoma* - *Ewing sarcoma* - *Acute lymphoblastic leukaemia* - *Wilms tumour* - *Burkitt lymphoma* - *Hodgkin lymphoma*

8.3 Hormones and antihormones

Complementary List

dexamethasone	***Oral liquid:*** *2 mg/5 mL.* - *Acute lymphoblastic leukaemia.*
hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* - *Acute lymphoblastic leukaemia.*
methylprednisolone	***Injection:*** *40 mg/ mL (as sodium succinate) in 1- mL single-dose vial and* *5- mL multi-dose vials; 80 mg/ mL (as sodium succinate) in 1- mL single-dose vial.* - *Acute lymphoblastic leukamia.*
☐ *prednisolone*	***Oral liquid:*** *5 mg/ mL.* ***Tablet:*** *5 mg; 25 mg.* - *Acute lymphoblastic leukaemia* - *Burkitt lymphoma* - *Hodgkin lymphoma*

~~9. ANTIPARKINSONISM MEDICINES~~

10. MEDICINES AFFECTING THE BLOOD

10.1 Antianaemia medicines

ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/ mL. **Tablet:** equivalent to 60 mg iron.
folic acid	**Tablet:** 1 mg; 5 mg.
hydroxocobalamin	**Injection:** 1 mg (as acetate, as hydrochloride **or** as sulfate) in 1- mL ampoule.
Complementary List	
☐ *erythropoiesis-stimulating agents**	***Injection: pre-filled syringe*** *1000IU/ 0.5 mL; 2000IU/ 0.5 mL; 3000IU/ 0.3 mL; 4000IU/ 0.4 mL; 5000IU/ 0.5 mL; 6000IU/ 0.6 mL; 8000IU/ 0.8mL; 10 000IU/ 1 mL; 20 000IU/ 0.5 mL; 40 000IU/ 1 mL* ** the square box applies to epoetin alfa, beta and theta, darbepoetin alfa, and their respective biosimilars*

10.2 Medicines affecting coagulation

phytomenadione	**Injection:** 1 mg/ mL; 10 mg/ mL in 5- mL ampoule. **Tablet:** 10 mg.
Complementary List	
desmopressin	***Injection:*** *4 micrograms/ mL (as acetate) in 1- mL ampoule.* ***Nasal spray:*** *10 micrograms (as acetate) per dose*
heparin sodium	***Injection:*** *1000 IU/mL; 5000 IU/mL in 1-mL ampoule.*
protamine sulfate	***Injection:*** *10 mg/ mL in 5- mL ampoule.*
☐ *warfarin*	***Tablet:*** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).*

10.3 Other medicines for haemoglobinopathies

Complementary List	
*deferoxamine**	***Powder for injection:*** *500 mg (mesilate) in vial.* ** Deferasirox oral form may be an alternative, depending on cost and availability.*
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 500 mg; 1 g.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh–frozen plasma

platelets

red blood cells

whole blood

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11.2.1 Human immunoglobulins

anti-rabies immunoglobulin	**Injection:** 150 IU/ mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	
normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.**
	Intravenous administration: *5%; 10% protein solution.***
	Subcutaneous administration: *15%; 16% protein solution.**
	** Indicated for primary immune deficiency.*
	***Indicated for primary immune deficiency and Kawasaki disease.*

11.2.2 Blood coagulation factors

Complementary List

☐ *coagulation factor VIII*	***Powder for injection:*** *500 IU/vial.*
☐ *coagulation factor IX*	***Powder for injection:*** *500 IU/vial, 1000 IU/vial.*

11.3 Plasma substitutes

☐ dextran 70*	**Injectable solution:** 6%.
	* Polygeline, injectable solution, 3.5% is considered as equivalent.

12. CARDIOVASCULAR MEDICINES	
~~**12.1 Antianginal medicines**~~	
~~**12.2 Antiarrhythmic medicines**~~	
12.3 Antihypertensive medicines	
☐ enalapril	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).
12.4 Medicines used in heart failure	
digoxin	**Injection:** 250 micrograms/ mL in 2- mL ampoule. **Oral liquid:** 50 micrograms/ mL. **Tablet:** 62.5 micrograms; 250 micrograms.
☐ furosemide	**Injection:** 10 mg/ mL in 2- mL ampoule. **Oral liquid:** 20 mg/5 mL. **Tablet:** 40 mg.
Complementary List	
dopamine	***Injection:*** *40 mg/ mL (hydrochloride) in 5- mL vial.*
~~**12.5 Antithrombotic medicines**~~	
~~**12.6 Lipid-lowering agents**~~	
~~**12.7 Fixed-dose combinations of cardiovascular medicines**~~	
13. DERMATOLOGICAL MEDICINES (topical)	
13.1 Antifungal medicines	
☐ miconazole	**Cream or ointment:** 2% (nitrate).
terbinafine	**Cream:** 1% **or Ointment:** 1% terbinafine hydrochloride.
13.2 Anti-infective medicines	
mupirocin	**Cream (as mupirocin calcium):** 2%. **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] >2 months.
13.3 Anti-inflammatory and antipruritic medicines	
☐ betamethasone [a]	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
☐ calamine	**Lotion.**

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*	
☐ hydrocortisone	**Cream or ointment:** 1% (acetate).
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	**Cream or lotion:** 5%.
coal tar	**Solution:** 5%.
☐ podophyllum resin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.
urea	**Cream or ointment:** 5%; 10%.
13.5 Scabicides and pediculicides	
☐ benzyl benzoate [a]	**Lotion:** 25%. [a] >2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.
14. DIAGNOSTIC AGENTS	
14.1 Ophthalmic medicines	
fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide	**Eye drops:** 0.5%.
14.2 Radiocontrast media	
Complementary List	
barium sulfate	***Aqueous suspension.***
15. DISINFECTANTS AND ANTISEPTICS	
15.1 Antiseptics	
☐ chlorhexidine	**Solution:** 5% (digluconate).
☐ ethanol	**Solution:** 70% (denatured).
☐ povidone iodine	**Solution:** 10% (equivalent to 1% available iodine).
15.2 Disinfectants	
alcohol based hand rub	**Solution:** containing ethanol 80% volume /volume **Solution:** containing isopropyl alcohol 75% volume/volume
☐ chlorine base compound	**Powder:** (0.1% available chlorine) for solution.
☐ chloroxylenol	**Solution:** 4.8%.
glutaral	**Solution:** 2%.

16. DIURETICS	
☐ furosemide	**Injection:** 10 mg/ mL in 2- mL ampoule. **Oral liquid:** 20 mg/5 mL. **Tablet:** 10 mg; 20 mg; 40 mg.
Complementary List	
☐ *hydrochlorothiazide*	***Tablet (scored):*** *25 mg.*
mannitol	***Injectable solution:*** *10%; 20%.*
spironolactone	***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.* ***Tablet:*** *25 mg.*
17. GASTROINTESTINAL MEDICINES	
Complementary List	
☐ *pancreatic enzymes*	*Age-appropriate formulations and doses including lipase, protease and amylase.*
17.1 Antiulcer medicines	
☐ omeprazole	**Powder for oral liquid:** 20 mg; 40 mg sachets. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
☐ ranitidine	**Injection:** 25 mg/ mL (as hydrochloride) in 2- mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).
17.2 Antiemetic medicines	
dexamethasone	**Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt). **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL. **Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide [a]	**Injection:** 5 mg (hydrochloride)/ mL in 2- mL ampoule. **Oral liquid:** 5 mg/5 mL. **Tablet:** 10 mg (hydrochloride). [a] Not in neonates.
ondansetron [a]	**Injection:** 2 mg base/ mL in 2- mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] >1 month.
~~**17.3 Anti-inflammatory medicines**~~	
17.4 Laxatives	

17. GASTROINTESTINAL MEDICINES *(continued)*

17.5 Medicines used in diarrhoea

17.5.1 Oral rehydration

oral rehydration salts

Powder for dilution in 200 mL; 500 mL; 1 L.

glucose:	75 mEq
sodium:	75 mEq or mmol/L
chloride:	65 mEq or mmol/L
potassium:	20 mEq or mmol/L
citrate:	10 mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

*trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

17.5.2 Medicines for diarrhoea

zinc sulfate*

Solid oral dosage form: 20 mg.

* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone — **Tablet:** 100 micrograms (acetate).

hydrocortisone — **Tablet:** 5 mg; 10 mg; 20 mg.

~~18.2 Androgens~~

~~18.3 Contraceptives~~

~~*18.3.1 Oral hormonal contraceptives*~~

~~18.3.2 Injectable hormonal contraceptives~~

~~*18.3.3 Intrauterine devices*~~

~~*18.3.4 Barrier methods*~~

~~*18.3.5 Implantable contraceptives*~~

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES *(continued)*

~~18.4 Estrogens~~

18.5 Insulins and other medicines used for diabetes

glucagon	**Injection:** 1 mg/ mL.
insulin injection (soluble)	**Injection:** 100 IU/mL in 10-mL vial.
intermediate-acting insulin	**Injection:** 100 IU/mL in 10-mL vial (as compound insulin zinc suspension **or** isophane insulin).
Complementary List	
metformin	***Tablet:*** *500 mg (hydrochloride).*

~~18.6 Ovulation inducers~~

~~18.7 Progestogens~~

18.8 Thyroid hormones and antithyroid medicines

levothyroxine	**Tablet:** 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).
Complementary List	
Lugol's solution	***Oral liquid:*** *about 130 mg total iodine/ mL.*
potassium iodide	***Tablet:*** *60 mg.*
propylthiouracil	***Tablet:*** *50 mg.*

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	**Injection.**

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements.

Anti-venom immunoglobulin*	**Injection.** * Exact type to be defined locally.
diphtheria antitoxin	Injection: 10 000 IU; 20 000 IU in vial.

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at 10 February 2017. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at:

http://www.who.int/immunization/documents/positionpapers/en/index.html.

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at:

http://www.who.int/immunization/policy/immunization_tables/en/index.html.

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

Recommendations for all
BCG vaccine
diphtheria vaccine
Haemophilus influenzae type b vaccine
hepatitis B vaccine
HPV vaccine
measles vaccine
pertussis vaccine

19. IMMUNOLOGICALS *(continued)*
pneumococcal vaccine
poliomyelitis vaccine
rotavirus vaccine
rubella vaccine
tetanus vaccine
Recommendations for certain regions
Japanese encephalitis vaccine
yellow fever vaccine
tick-borne encephalitis vaccine
Recommendations for some high-risk populations
cholera vaccine
hepatitis A vaccine
meningococcal meningitis vaccine
rabies vaccine
typhoid vaccine
Recommendations for immunization programmes with certain characteristics
influenza vaccine (seasonal)
mumps vaccine
varicella vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
neostigmine	**Injection:** 500 micrograms in 1- mL ampoule; 2.5 mg (metilsulfate) in 1- mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg (chloride)/ mL in 2- mL ampoule. **Powder for injection** (chloride), in vial.
☐ vecuronium	**Powder for injection:** 10 mg (bromide) in vial.

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS *(continued)*

Complementary List	
pyridostigmine	***Injection:*** *1 mg in 1- mL ampoule.* ***Tablet:*** *60 mg (bromide).*

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% W/W.
azithromycin	**Solution (eye drops):** 1.5%.
erythromycin*	**Ointment:** 0.5% *Infections due to Chlamydia trachomatis or Neisseria gonorrhoea.
☐ gentamicin	**Solution (eye drops):** 0.3% (sulfate).
natamycin	**Suspension:** (eye drops): 5%
☐ ofloxacin	**Solution (eye drops):** 0.3%.
☐ tetracycline	**Eye ointment:** 1% (hydrochloride).

21.2 Anti-inflammatory agents

☐ prednisolone	**Solution (eye drops):** 0.5% (sodium phosphate).

21.3 Local anaesthetics

☐ tetracaine [a]	**Solution (eye drops):** 0.5% (hydrochloride). [a] Not in preterm neonates.

~~21.4 Miotics and antiglaucoma medicines~~

21.5 Mydriatics

atropine* [a]	**Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate). * **Or** homatropine (hydrobromide) **or** cyclopentolate (hydrochloride). [a] >3 months.
Complementary List	
epinephrine (adrenaline)	***Solution (eye drops):*** *2% (as hydrochloride).*

~~22. OXYTOCICS AND ANTIOXYTOCICS~~

~~22.1 Oxytocics~~

~~22.2 Antioxytocics (tocolytics)~~

23. PERITONEAL DIALYSIS SOLUTION

Complementary List

intraperitoneal dialysis solution (of appropriate composition)	***Parenteral solution.***

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines used in psychotic disorders

Complementary List

chlorpromazine	***Injection:*** *25 mg (hydrochloride)/ mL in 2- mL ampoule.* ***Oral liquid:*** *25 mg (hydrochloride)/5 mL.* ***Tablet:*** *10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).*
haloperidol	***Injection:*** *5 mg in 1- mL ampoule.* ***Oral liquid:*** *2 mg/ mL.* ***Solid oral dosage form:*** *0.5 mg; 2 mg; 5 mg.*

24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders

Complementary List

fluoxetine [a]	***Solid oral dosage form:*** *20 mg (as hydrochloride).* [a] *>8 years.*

24.2.2 Medicines used in bipolar disorders

24.3 Medicines for anxiety disorders

24.4 Medicines used for obsessive compulsive disorders

24.5 Medicines for disorders due to psychoactive substance use

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines

☐ budesonide	**Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1- mL ampoule.

25. MEDICINES ACTING ON THE RESPIRATORY TRACT *(continued)*	
☐ salbutamol	**IInjection:** 50 micrograms (as sulfate)/mL in 5-mL ampoule. **Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose. **Respirator solution for use in nebulizers:** 5 mg (as sulfate)/ mL.

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**
26.2 Parenteral	
glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L).
potassium chloride	**Solution for dilution:** 7.5% (equivalent to K+ 1 mmol/mL and Cl- 1 mmol/mL); 15% (equivalent to K+ 2 mmol/mL and Cl- 2 mmol/mL).
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+167 mmol/L, HCO3- 167 mmol/L). **Solution:** 8.4% in 10-mL ampoule (equivalent to Na+ 1000 mmol/L, HCO3-1000 mmol/L).
☐ sodium lactate, compound solution	**Injectable solution.**
26.3 Miscellaneous	
water for injection	2- mL; 5- mL; 10- mL ampoules.

27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.

27. VITAMINS AND MINERALS *(continued)*	
colecalciferol	**Oral liquid:** 400 IU/ mL. **Solid oral dosage form:** 400 IU; 1000 IU. * Ergocalciferol can be used as an alternative.
iodine	**Capsule:** 200 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
pyridoxine	**Tablet:** 25 mg (hydrochloride).
retinol	**Capsule:** 100 000 IU; 200 000 IU (as palmitate). **Oral oily solution:** 100 000 IU (as palmitate)/mL in multidose dispenser. **Tablet (sugar-coated):** 10 000 IU (as palmitate). **Water-miscible injection:** 100 000 IU (as palmitate) in 2- mL ampoule.
riboflavin	**Tablet:** 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	**Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:*** *100 mg/ mL in 10- mL ampoule.*
28. EAR, NOSE AND THROAT MEDICINES	
acetic acid	**Topical:** 2%, in alcohol.
☐ budesonide	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin	**Topical:** 0.3% drops (as hydrochloride).
☐ xylometazoline [a]	**Nasal spray:** 0.05%. [a] Not in children less than 3 months.
29. SPECIFIC MEDICINES FOR NEONATAL CARE	
29.1 Medicines administered to the neonate	
caffeine citrate	**Injection:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL). **Oral liquid:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL).
chlorhexidine	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).

29. SPECIFIC MEDICINES FOR NEONATAL CARE *(continued)*	
Complementary List	
☐ *ibuprofen*	***Solution for injection:*** *5 mg/ mL.*
☐ *prostaglandin E*	***Solution for injection:***
	Prostaglandin E1: *0.5 mg/ mL in alcohol.*
	Prostaglandin E 2: *1 mg/ mL.*
surfactant	***Suspension for intratracheal instillation:*** *25 mg/ mL or 80 mg/ mL.*
30. MEDICINES FOR DISEASES OF JOINTS	
~~**30.1 Medicines used to treat gout**~~	
30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)	
Complementary List	
hydroxychloroquine [c]	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium salt).*
30.3 Juvenile joint diseases	
acetylsalicylic acid* (acute or chronic use)	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg. * For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

Annex 3

The Anatomical Therapeutic Chemical (ATC) Classification System

The following list provides the corresponding Anatomical Therapeutic Chemical (ATC) classification codes for all items on the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children, sorted by ATC code number.

ATC code	ATC group/medicine or item	Section
A	**ALIMENTARY TRACT AND METABOLISM**	
A02	**Drugs for acid related disorders**	
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	
A02BA	*H2-receptor antagonists*	
A02BA02	ranitidine	17.1
A02BC	*Proton pump inhibitors*	
A02BC01	omeprazole	17.1
A03	**Drugs for functional gastrointestinal disorders**	
A03B	Belladonna and derivatives, plain	
A03BA	*Belladonna alkaloids, tertiary amines*	
A03BA01	atropine	1.3; 4.2
A03BB	*Belladonna alkaloids, semisynthetic, quaternary ammonium compounds*	
A03BB01	*hyoscine butylbromide**	2.3
A03F	Propulsives	
A03FA	*Propulsives*	
A03FA01	metoclopramide	2.3; 17.2
A04	**Antiemetics and antinauseants**	
A04A	Antiemetics and antinauseants	
A04AA	*Serotonin (5HT3) antagonists*	
A04AA01	ondansetron	17.2
A04AD	*Other antiemetics*	
A04AD01	hyoscine hydrobromide*	2.3

ATC code	ATC group/medicine or item	Section
A06	**Laxatives**	
A06A	Laxatives	
A06AA	*Softeners, emollients*	
A06AA02	docusate sodium	2.3
A06AB	*Contact laxatives*	
A06AB06	senna glycosides*	17.4
A06AD	*Osmotically acting laxatives*	
A06AD11	lactulose	2.3
A07	**Antidiarrheals, intestinal antiinflammatory/antiinfective agents**	
A07A	Intestinal antiinfectives	
A07AA	*Antibiotics*	
A07AA06	paromomycin	6.5.2
A07B	Intestinal adsorbents	
A07BA	*Charcoal preparations*	
A07BA01	medicinal charcoal*	4.1
A07C	Electrolytes with carbohydrates	
A07CA	*Oral rehydration salt formulations**	17.5.1; 26.1
A07DA	*Antipropulsives*	
A07DA03	loperamide	2.3
A07E	Intestinal antiinflammatory agents	
A07EA	*Corticosteroids for local use*	
A07EA02	hydrocortisone	17.3
A07EC	*Aminosalicylic acid and similar agents*	
A07EC01	sulfasalazine	17.3; 30.2
A09	**Digestives, incl. enzymes**	
A09A	Digestives, incl. enzymes	
A09AA	*Enzyme preparations*	
A09AA02	multienzymes (lipase, protease, etc.)*	17

ATC code	ATC group/medicine or item	Section
A10	**Drugs used in diabetes**	
A10A	Insulins and analogues	
A10AB	*Insulins and analogues for injection, fast-acting*	
A10AB	insulin injection (soluble)*	18.5
A10AC	*Insulins and analogues for injection, intermediate-acting*	
A10AC	insulin, intermediate-acting*	18.5
A10B	Blood glucose lowering drugs, excl. insulins	
A10BA	*Biguanides*	
A10BA02	metformin	18.5
A10BB	*Sulfonamides, urea derivatives*	
A10BB01	glibenclamide	18.5
A10BB09	gliclazide	18.5
A11	**Vitamins**	
A11C	Vitamin A and D, incl. combinations of the two	
A11CA	*Vitamin A, plain*	
A11CA01	retinol	27
A11CC	*Vitamin D and analogues*	
A11CC01	ergocalciferol	27
A11CC05	cholecalciferol*	27
A11D	Vitamin B1, plain and in combination with vitamin B6 and B12	
A11DA	*Vitamin B1, plain*	
A11DA01	thiamine	27
A11G	Ascorbic acid (vitamin C), incl. combinations	
A11GA	*Ascorbic acid (vitamin C), plain*	
A11GA01	ascorbic acid	27
A11H	Other plain vitamin preparations	
A11HA	*Other plain vitamin preparations*	
A11HA01	nicotinamide	27
A11HA02	pyridoxine	27
A11HA04	riboflavin	27

ATC code	ATC group/medicine or item	Section
A12	**Mineral supplements**	
A12A	Calcium	
A12AA	*Calcium*	
A12AA03	calcium gluconate	4.2; 27
A12C	Other mineral supplements	
A12CB	*Zinc*	
A12CB01	zinc sulfate	17.5.2
A12CD	*Fluoride*	
A12CD01	sodium fluoride	27
A12CX	*Other mineral products**	27
B	**BLOOD AND BLOOD FORMING ORGANS**	
B01	**Antithrombotic agents**	
B01A	Antithrombotic agents	
B01AA	*Vitamin K antagonists*	
B01AA03	warfarin	10.2
B01AB	*Heparin group*	
B01AB01	heparin*	10.2
B01AB04	dalteparin	10.2
B01AB05	enoxaparin	10.2
B01AB06	nadroparin	10.2
B01AC	*Platelet aggregation inhibitors excl. heparin*	
B01AC04	clopidogrel	12.5.1
B01AC06	acetylsalicylic acid	7.1; 12.5.1; 30.3
B01AD	*Enzymes*	
B01AD01	streptokinase	12.5.2
B02	**Antihemorrhagics**	
B02A	Antifibrinolytics	
B02AA	*Amino acids*	

ATC code	ATC group/medicine or item	Section
B02AA02	tranexamic acid	10.2
B02B	Vitamin K and other hemostatics	
B02BA	*Vitamin K*	
B02BA01	phytomenadione	10.2
B02BD	*Blood coagulation factors*	
B02BD01	coagulation factor IX, II, VII and X in combination*	11.2.2
B02BD02	coagulation factor VIII*	11.2.2
B03	**Antianemic preparations**	
B03A	Iron preparations	10.1
B03AA	*Iron bivalent, oral preparations**	10.1
B03AB	*Iron trivalent, oral preparations**	10.1
B03AD	*Iron in combination with folic acid**	10.1
B03B	Vitamin B12 and folic acid	
B03BA	*Vitamin B12 (cyanocobalamin and analogues)*	
B03BA03	hydroxocobalamin	10.1
B03BB	*Folic acid and derivatives*	
B03BB01	folic acid	10.1
B03X	*Other antianemic preparations*	
B03XA	Other antianemic preparations	
B03XA01	erythropoietin	10.1
B03XA02	darbepoetin alfa	10.1
B03XA03	methoxy polyethylene glycol-epoetin beta	10.1
B05	**Blood substitutes and perfusion solutions**	
B05A	Blood and related products	
B05A	platelet concentrates	11.1
B05A	whole blood*	11.1
B05AA	*Blood substitutes and plasma protein fractions*	
B05AA05	dextran*	11.3
B05AX	*Other blood products*	
B05AX01	red blood cells*	11.1
B05AX03	fresh frozen plasma*	11.1

ATC code	ATC group/medicine or item	Section
B05B	I.V. solutions	
B05BA	*Solutions for parenteral nutrition*	
B05BA03	carbohydrates*	26.2
B05BB	*Solutions affecting the electrolyte balance*	
B05BB01	electrolytes*	26.2
B05BB02	electrolytes with carbohydrates*	26.2
B05BC	*Solutions producing osmotic diuresis*	
B05BC01	mannitol	16
B05D	Peritoneal dialytics	
B05DA	*Isotonic solutions**	23
B05X	I.V. solution additives	
B05XA	*Electrolyte solutions*	
B05XA01	potassium chloride	26.1; 26.2
B05XA02	sodium bicarbonate*	26.2
B05XA03	sodium chloride	26.2
B05XA05	magnesium sulfate	5
C	**CARDIOVASCULAR SYSTEM**	
C01	**Cardiac therapy**	
C01A	Cardiac glycosides	
C01AA	*Digitalis glycosides*	
C01AA05	digoxin	12.2; 12.4
C01B	Antiarrhythmics, class I and III	
C01BB	*Antiarrhythmics, class Ib*	
C01BB01	lidocaine	12.2
C01BD	*Antiarrhythmics, class III*	
C01BD01	amiodarone	12.2
C01C	Cardiac stimulants excl. cardiac glycosides	
C01CA	*Adrenergic and dopaminergic agents*	
C01CA04	dopamine	12.4
C01CA24	epinephrine (adrenaline)	3; 12.2; 25.1
C01CA26	ephedrine	1.2

ATC code	ATC group/medicine or item	Section
C01D	Vasodilators used in cardiac diseases	
C01DA	*Organic nitrates*	
C01DA02	glyceryl trinitrate	12.1
C01DA08	isosorbide dinitrate	12.1
C02	Antihypertensives	
C02A	*Antiadrenergic agents, centrally acting*	
C02AB	*Methyldopa*	
C02AB01	methyldopa (levorotatory)*	12.3
C02D	Arteriolar smooth muscle, agents acting on	
C02DB	*Hydrazinophthalazine derivatives*	
C02DB02	hydrazaline	12.3
C02DD	*Nitroferricyanide derivatives*	
C02DD01	nitroprusside*	12.3
C03	**Diuretics**	
C03A	Low-ceiling diuretics, thiazides	
C03AA	*Thiazides, plain*	
C03AA03	hydrochlorothiazide	12.3; 12.4; 16
C03C	High-ceiling diuretics	
C03CA	*Sulfonamides, plain*	
C03CA01	furosemide	12.4; 16
C03D	Potassium-sparing agents	
C03DA	*Aldosterone antagonists*	
C03DA01	spironolactone	12.4; 16
C03DB	*Other potassium-sparing agents*	
C03DB01	amiloride	16
C07	**Beta blocking agents**	
C07A	Beta blocking agents	
C07AA	*Beta blocking agents, non-selective*	
C07AA05	propranolol	7.2

ATC code	ATC group/medicine or item	Section
C07AB	*Beta blocking agents, selective*	
C07AB02	metoprolol	12.1; 12.2; 12.3; 12.4
C07AB03	atenolol	12.3
C07AB07	bisoprolol	12.1; 12.2; 12.3; 12.4
C07AG	*Alpha and beta blocking agents*	
C07AG02	carvedilol	12.1; 12.2; 12.3; 12.4
C08	**Calcium channel blockers**	
C08C	Selective calcium channel blockers with mainly vascular effects	
C08CA	*Dihydropyridine derivatives*	
C08CA01	amlodipine	12.3
C08CA05	nifedipine	22.2
C08D	Selective calcium channel blockers with direct cardiac effects	
C08DA	*Phenylalkylamine derivatives*	
C08DA01	verapamil	12.1; 12.2
C09	**Agents acting on the renin-angiotensin system**	
C09A	ACE inhibitors, plain	
C09AA	*ACE inhibitors, plain*	
C09AA02	enalapril	12.3; 12.4
C09C	Antiotensin II antagonists, plain	
C09CA	*Antiotensin II antagonists, plain*	
C09CA01	losartan	12.3; 12.4
C10	**Lipid modifying agents**	
C10A	Lipid modifying agents, plain	
C10AA	*HMG CoA reductase inhibitors*	
C10AA01	simvastatin	12.6

ATC code	ATC group/medicine or item	Section
D	**DERMATOLOGICALS**	
D01	**Antifungals for dermatological use**	
D01A	Antifungals for topical use	
D01AA	*Antibiotics*	
D01AA01	nystatin	6.3
D01AC	*Imidazole and triazole derivatives*	
D01AC02	miconazole	13.1
D01AE	*Other antifungals for topical use*	
D01AE12	salicylic acid	13.4
D01AE13	selenium sulfide	13.1
D01B	Antifungals for systemic use	
D01BA	*Antifungals for systemic use*	
D01BA01	griseofulvin	6.3
D01BA02	terbinafine	13.1
D02	**Emollients and protectives**	
D02A	*Emollients and protectives*	
D02AB	*Zinc products**	13.3
D02AE	*Carbamide products*	
D02AE01	carbamide*	13.4
D05	**Antipsoriatics**	
D05A	Antipsoriatics for topical use	
D06	**Antibiotics and chemotherapeutics for dermatological use**	
D06A	Antibiotics for topical use	
D06AX	*Other antibiotics for topical use*	
D06AX09	mupirocin	13.2
D06B	Chemotherapeutics for topical use	
D06BA	*Sulfonamides*	
D06BA01	silver sulfadiazine	13.2
D06BB	*Antivirals*	

ATC code	ATC group/medicine or item	Section
D06BB04	podophyllotoxin*	13.4
D07	**Corticosteroids, dermatological preparations**	
D07A	Corticosteroids, plain	
D07AA	*Corticosteroids, weak (group I)*	
D07AA02	hydrocortisone	13.3
D07AC	*Corticosteroids, potent (group III)*	
D07AC01	betamethasone	13.3
D08	**Antiseptics and disinfectants**	
D08A	Antiseptics and disinfectants	
D08AC	*Biguanides and amidines*	
D08AC02	chlorhexidine	15.1; 29.1
D08AE	*Phenol and derivatives*	
D08AE05	chloroxylenol	15.2
D08AG	*Iodine products*	
D08AG02	povidone-iodine	15.1
D08AX	*Other antiseptics and disinfectants**	15
D08AX05	isopropanol*	15.2
D08AX06	potassium permanganate	13.2
D08AX08	ethanol	15.1; 15.2
D10	**Anti-acne preparations**	
D10A	Anti-acne preparations for topical use	
D10AE	*Peroxides*	
D10AE01	benzoyl peroxide	13.4
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	
G01	**Gynecological antiinfectives and antiseptics**	
G01A	Antiinfectives and antiseptics, excl. combinations with corticosteroids	

ATC code	ATC group/medicine or item	Section
G01AF	*Imidazole derivatives*	
G01AF02	clotrimazole	6.3
G02	**Other gynecologicals**	
G02A	Oxytocics	
G02AB	*Ergot alkaloids*	
G02AB03	ergometrine	22.1
G02AD	*Prostaglandins*	
G02AD06	misoprostol	22.1
G02B	Contraceptives for topical use	
G02BA	*Intrauterine contraceptives*	
G02BA02	plastic IUD with copper*	18.3.3
G02BA03	plastic IUD with progesteron*	18.3.3
G02BB	*Intravaginal contraceptives**	18.3.4; 18.3.6
G03	**Sex hormones and modulators of the genital system**	
G03A	Hormonal contraceptives for systemic use	
G03AA	*Progestogens and estrogens, fixed combinations*	
G03AA05	norethisterone and ethinylestradiol	18.3.1
G03AA07	levonorgestrel and ethinylestradiol	18.3.1
G03AA08	*medroxyprogesterone and estrogen**	18.3.2
G03AB	*Progestogens and estrogens, sequential preparations*	
G03AB03	levonorgestrel and estrogen*	18.3.1
G03AC	*Progestogens*	
G03AC01	norethisterone*	18.3.2
G03AC03	levonorgestrel	18.3.1; 18.3.3; 18.3.5
G03AC06	medroxyprogesterone*	18.3.2; 18.7
G03AC08	etonorgestrel	18.3.5
G03AD	*Emergency contraceptives*	
G03AD01	levonorgestrel	18.3.1

ATC code	ATC group/medicine or item	Section
G03AD02	ulipristal	18.3.1
G03B	Androgens	
G03BA	3-oxoandrosten (4) derivatives	
G03BA03	testosterone	18.2
G03D	*Progestogens*	
G03DA	*Pregnen (4) derivatives*	
G03DA04	progesterone	18.3.6
G03G	Gonadotropins and other ovulation stimulants	
G03GB	*Ovulation stimulants, synthetic*	
G03GB02	clomifene	18.6
G03X	Other sex hormones and modulators of the genital system	
G03XB	*Antiprogesterons*	
G03XB01	mifepristone	22.1
H	**SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS**	
H01	**Pituitary, hypothalamic hormones and analogues**	
H01B	Posterior pituitary lobe hormones	
H01BA	*Vasopressin and analogues*	
H01BA02	desmopressin	10.2
H01BB	*Oxytocin and analogues*	
H01BB02	oxytocin	22.1
H02	**Corticosteroids for systemic use**	
H02A	Corticosteroids for systemic use, plain	
H02AA	*Mineralocorticoids*	
H02AA02	fludrocortisone	18.1
H02AB	*Glucocorticoids*	
H02AB02	dexamethasone	2.3; 3; 8.3; 17.2; 29.2
H02AB04	methylprednisolone	8.3
H02AB06	prednisolone	3; 8.3
H02AB09	hydrocortisone	3; 8.3

ATC code	ATC group/medicine or item	Section
H03	**Thyroid therapy**	
H03A	Thyroid preparations	
H03AA	*Thyroid hormones*	
H03AA01	levothyroxine sodium*	18.8
H03B	Antithyroid preparations	
H03BA	*Thiouracils*	
H03BA02	propylthiouracil	18.8
H03C	Iodine therapy	
H03CA	*Iodine therapy**	18.8
H04	**Pancreatic hormones**	
H04A	Glycogenolytic hormones	
H04AA	*Glycogenolytic hormones*	
H04AA01	glucagon	18.5
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	
J01	**Antibacterials for systemic use**	
J01A	Tetracyclines	
J01AA	*Tetracyclines*	
J01AA02	doxycycline	6.2.2; 6.5.3.1; 6.5.3.2
J01AA12	tigecycline	6.2.2
J01B	Amphenicols	
J01BA	*Amphenicols*	
J01BA01	chloramphenicol	6.2.2
J01C	Beta-lactam antibacterials, penicillins	
J01CA	*Penicillins with extended spectrum*	
J01CA01	ampicillin	6.2.1
J01CA04	amoxicillin	6.2.1
J01CE	*Beta-lactamase sensitive penicillins*	

ATC code	ATC group/medicine or item	Section
J01CE01	benzylpenicillin	6.2.1
J01CE02	phenoxymethylpenicillin	6.2.1
J01CE08	benzathine benzylpenicillin	6.2.1
J01CE09	procaine benzylpenicillin	6.2.1
J01CF	*Beta-lactamase resistant penicillins*	
J01CF02	cloxacillin	6.2.1
J01CR	*Combinations of penicillins, incl. beta-lactamase inhibitors*	
J01CR02	amoxicillin and enzyme inhibitor*	6.2.1
J01CR05	piperacillin and enzyme inhibitor*	6.2.1
J01D	Other beta-lactam antibacterials	
J01DB	*First-generation cephalosporins*	
J01DB01	cefalexin	6.2.1
J01DB04	cefazolin	6.2.1
J01DD	*Third-generation cephalosporins*	
J01DD01	cefotaxime	6.2.1
J01DD02	ceftazidime	6.2.1
J01DD04	ceftriaxone	6.2.1
J01DD08	cefixime	6.2.1
J01DE	*Fourth generation cephalosporins*	
J01DE01	cefepime	6.2.1
J01DF	*Monobactams*	
J01DF01	Aztreonam	6.2.1
J01DH	*Carbapenems*	
J01DH02	meropenem	6.2.1
J01DH51	imipenem and enzyme inhibitor*	6.2.1
J01DI	*Other cephalosporins and penems*	
J01DI02	ceftoraline	6.2.1
J01E	Sulfonamides and trimethoprim	
J01EA	*Trimethoprim and derivatives*	
J01EA01	trimethoprim	6.2.2
J01EC	*Intermediate-acting sulfonamides*	
J01EC02	sulfadiazine	6.5.4
J01EE	*Combinations of sulfonamides and trimethoprim, incl. derivatives*	

ATC code	ATC group/medicine or item	Section
J01EE01	sulfamethoxazole + trimethoprim	6.2.2; 6.5.4
J01F	Macrolides, lincosamides and streptogramins	
J01FA	Macrolides	
J01FA01	*erythromycin*	6.2.2
J01FA09	clarithromycin	6.2.2
J01FA10	azithromycin	6.2.2; 21.1
J01FF	*Lincosamides*	
J01FF01	clindamycin	6.2.2
J01G	Aminoglycoside antibacterials	
J01GA	*Streptomycins*	
J01GA01	streptomycin	6.2.4
J01GB	*Other aminoglycosides*	
J01GB03	gentamicin	6.2.2
J01GB04	kanamycin	6.2.4
J01GB06	amikacin	6.2.2; 6.2.4
J01M	Quinolone antibacterials	
J01MA	*Fluoroquinolones*	
J01MA01	ofloxacin	21.1
J01MA02	ciprofloxacin	6.2.2
J01MA12	levofloxacin	6.2.4
J01MA14	moxifloxacin	6.2.4
J01X	Other antibacterials	
J01XA	*Glycopeptide antibacterials*	
J01XA01	vancomycin	6.2.2
J01XB	*Polymyxins*	
J01XB01	colistin	6.2.2
J01XD	*Imidazole derivatives*	
J01XD01	metronidazole	6.2.2; 6.5.1
J01XE	*Nitrofuran derivatives*	
J01XE01	nitrofurantoin	6.2.2
J01XX	*Other antibacterials*	
J01XX01	fosfomycin	6.2.2
J01XX04	spectinomycin	6.2.2

ATC code	ATC group/medicine or item	Section
J01XX08	linezolid	6.2.2; 6.2.4
J01XX09	daptomycin	6.2.2
J02	**Antimycotics for systemic use**	
J02A	Antimycotics for systemic use	
J02AA	*Antibiotics*	
J02AA01	amphotericin B	6.3; 6.5.2
J02AC	*Triazole derivatives*	
J02AC01	fluconazole	6.3
J02AC02	itraconazole	6.3
J02AC03	voriconazole	6.3
J02AX	*Other antimycotics for systemic use*	
J02AX01	flucytosine	6.3
J04	**Antimycobacterials**	
J04A	Drugs for treatment of tuberculosis	
J04AA	*Aminosalicylic acid and derivatives*	
J04AA01	p-aminosalicylic acid*	6.2.4
J04AB	*Antibiotics*	
J04AB01	cycloserine	6.2.4
J04AB02	rifampicin	6.2.3; 6.2.4
J04AB04	rifabutin	6.2.4
J04AB05	rifapentine	6.2.4
J04AB30	capreomycin	6.2.4
J04AC	*Hydrazides*	
J04AC01	isoniazid	6.2.4
J04AC51	isoniazid, combinations	6.4.2.5
J04AD	*Thiocarbamide derivatives*	
J04AD03	ethionamide	6.2.4
J04AD01	protionamide	6.2.4
J04AK	*Other drugs for treatment of tuberculosis*	
J04AK01	pyrazinamide	6.2.4
J04AK02	ethambutol	6.2.4

ATC code	ATC group/medicine or item	Section
J04AK03	terizidone	6.2.4
J04AK05	bedaquiline	6.2.4
J04AK06	delamanid	6.2.4
J04AM	*Combinations of drugs for treatment of tuberculosis**	6.2.4
J04AM02	rifampicin and isoniazid*	6.2.4
J04AM03	ethambutol and isoniazid*	6.2.4
J04AM05	rifampicin, pyrazinamide and isoniazid*	6.2.4
J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid*	6.2.4
J04B	Drugs for treatment of lepra	
J04BA	*Drugs for treatment of lepra*	
J04BA01	clofazimine	6.2.3; 6.2.4
J04BA02	dapsone	6.2.3
J05	**Antivirals for systemic use**	
J05A	Direct acting antivirals	
J05AB	*Nucleosides and nucleotides excl. reverse transcriptase inhibitors*	
J05AB01	aciclovir	6.4.1
J05AB04	ribavirin	6.4.3; 6.4.4.2.5
J05AB14	valganciclovir	6.4.3
J05AE	*Protease inhibitors*	
J05AE03	ritonavir (r)	6.4.2.3
J05AE08	atazanavir	6.4.2.3
J05AE10	darunavir	6.4.2.3
J05AE14	simeprevir	6.4.4.2.2
J05AF	*Nucleoside and nucleotide reverse transcriptase inhibitors*	
J05AF01	zidovudine (ZDV or AZT)	6.4.2.1
J05AF05	lamivudine (3TC)	6.4.2.1
J05AF06	abacavir (ABC)	6.4.2.1
J05AF07	tenofovir disoproxil	6.4.2.1
J05AF10	entecavir	6.4.4.1.1
J05AG	*Non-nucleoside reverse transcriptase inhibitors*	

ATC code	ATC group/medicine or item	Section
J05AG01	nevirapine (NVP)	6.4.2.2
J05AG03	efavirenz (EFV or EFZ)	6.4.2.2
J05AH	*Neuraminidase inhibitors*	
J05AH02	oseltamivir	6.4.3
J05AR	*Antivirals for treatment of HIV infections, combinations*	
J05AR01	lamivudine + zidovudine (ZDV or AZT)	6.4.2
J05AR02	abacavir + lamivudine	6.4.2
J05AR03	tenofovir disoproxil + emtricitabine	6.4.2
J05AR05	lamivudine + nevirapine + zidovudine	6.4.2
J05AR06	emtricitabine + tenofovir disoproxil + efavirenz	6.4.2
J05AR10	lopinavir + ritonavir (LPV/r)*	6.4.2.3
J05AR11	lamivudine + tenofovir disoproxil + efavirenz	6.4.2
J05ARxx	atazanavir + ritonavir	6.4.2.3
J05AX	*Other antivirals*	
J05AX08	raltegravir	6.4.2.4
J06AX12	dolutegravir	6.4.2.4
J05AX14	daclatasvir	6.4.4.2.3
J05AX15	sofosbuvir	6.4.4.2.1
J05AX16	dasabuvir	6.4.4.2.4
J05AX65	ledipasvir + sofosbuvir	6.4.4.2
J05AX66	ombitasvir + paritaprevir + ritonavir	6.4.4.2
J05AX69	sofosbuvir + velpatasvir	6.4.4.2

J06	Immune sera and immunoglobulins	
J06A	Immune sera	
J06AA	*Immune sera*	
J06AA01	diphtheria antitoxin	19.2
J06AA03	snake venom antiserum*	19.2
J06B	Immunoglobulins	
J06BA	*Immunoglobulins, normal human*	
J06BA01	immunoglobulins, normal human, for extravascular admin*	11.2.1
J06BA02	immunoglobulins, normal human, for intravascular admin*	11.2.1
J06BB	*Specific immunoglobulins*	

ATC code	ATC group/medicine or item	Section
J06BB01	anti-D immunoglobulin	11.2.1
J06BB02	tetanus immunoglobulin*	11.2.1
J06BB05	rabies immunoglobulin*	11.2.1
J07	**Vaccines**	
J07A	Bacterial vaccines	
J07AE	*Cholera vaccines**	19.3
J07AF	*Diphtheria vaccines*	
J07AF01	diphtheria toxoid*	19.3
J07AG	*Hemophilus influenzae B vaccines*	
J07AG01	hemophilus influenzae B, purified antigen conjugated*	19.3
J07AH	*Meningococcal vaccines**	19.3
J07AJ	*Pertussis vaccines*	
J07AJ01	pertussis vaccine	19.3
J07AL	*Pneumococcal vaccines*	
J07AL01	pneumococcus, purified polysaccharides antigen*	19.3
J07AM	*Tetanus vaccines*	
J07AM01	tetanus toxoid*	19.3
J07AN	*Tuberculosis vaccines*	
J07AN01	tuberculosis, live attenuated*	19.3
J07AP	*Typhoid vaccines**	19.3
J07B	Viral vaccines	
J07BA	*Encephalitis vaccines*	
J07BA01	encephalitis, tick-borne, inactivated, whole virus	19.3
J07BA02	encephalitis, Japanese, inactivated, whole virus	19.3
J07BB	*Influenza vaccines**	19.3
J07BC	*Hepatitis vaccines*	
J07BC01	hepatitis B vaccine	19.3
J07BC02	hepatitis A vaccine	19.3
J07BD	*Measles vaccine**	
J07BD01	measles vaccine, live attenuated*	19.3
J07BE	*Mumps vaccines*	
J07BE01	mumps vaccine, live attenuated*	19.3

ATC code	ATC group/medicine or item	Section
J07BF	*Poliomyelitis vaccine*	19.3
J07BG	*Rabies vaccine*	19.3
J07BH	*Rota virus diarrhea vaccines**	19.3
J07BJ	*Rubella vaccines*	19.3
J07BK	*Varicella zoster vaccines**	19.3
J07BL	*Yellow fever vaccines*	19.3
J07BM	*Papillomavirus vaccines*	
J07BM01	papillomavirus (human types 6, 11, 16, 18)*	19.3
J07BM02	papillomavirus (human types 16, 18)*	19.3
J07C	Bacterial and viral vaccines, combined	
J07CA	*Bacterial and viral vaccines, combined**	19.3
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	
L01	**Antineoplastic agents**	
L01A	Alkylating agents	
L01AA	*Nitrogen mustard analogues*	
L01AA01	cyclophosphamide	8.2
L01AA02	chlorambucil	8.2
L01AA09	bendamustine	8.2
L01AA06	ifosfamide	8.2
L01AX	*Other alkylating agents*	
L01AX04	dacarbazine	8.2
L01B	Antimetabolites	
L01BA	*Folic acid analogues*	
L01BA01	methotrexate	8.2; 30.2
L01BB	*Purine analogues*	
L01BB02	mercaptopurine	8.2
L01BB03	tioguanine	8.2
L01BB05	fludarabine	8.2
L01BC	*Pyrimidine analogues*	
L01BC01	cytarabine	8.2
L01BC02	fluorouracil	8.2; 13.4
L01BC05	gemcitabine	8.2

ATC code	ATC group/medicine or item	Section
L01BC06	capecitabine	8.2
L01C	Plant alkaloids and other natural products	
L01CA	*Vinca alkaloids and analogues*	
L01CA01	vinblastine	8.2
L01CA02	vincristine	8.2
L01CA04	vinorelbine	8.2
L01CB	*Podophyllotoxin derivatives*	
L01CB01	etoposide	8.2
L01CD	*Taxanes*	
L01CD01	paclitaxel	8.2
L01CD02	docetaxel	8.2
L01D	Cytotoxic antibiotics and related substances	
L01DA	*Actinomycines*	
L01DA01	dactinomycin	8.2
L01DB	*Anthracyclines and related substances*	
L01DB01	doxorubicin	8.2
L01DB02	daunorubicin	8.2
L01DC	*Other cytotoxic antibiotics*	
L01DC01	bleomycin	8.2
L01X	Other antineoplastic agents	
L01XA	*Platinum compounds*	
L01XA01	cisplatin	8.2
L01XA02	carboplatin	8.2
L01XA03	oxaliplatin	8.2
L01XB	*Methylhydrazines*	
L01XB01	procarbazine	8.2
L01X	*Other antineoplastic agents*	
L01XC	*Monoclonal antibodies*	
L01XC02	rituximab	8.2
L01XC03	trastuzumab	8.2
L01XC07	bevacizumab	21.6
L01XE	*Protein kinase inhibitors*	
L01XE01	imatinib	8.2

ATC code	ATC group/medicine or item	Section
L01XE06	dasatinib	8.2
L01XE08	nilotinib	8.2
L01XX	*Other antineoplastic agents*	
L01XX02	asparaginase	8.2
L01XX05	hydroxycarbamide	8.2; 10.3
L01XX09	miltefosine	6.5.2
L01XX14	tretinoin*	8.2
L01XX19	irinotecan	8.2
L02	*Endocrine therapy*	
L02A	*Hormones and related agents*	
L02AE	Gonadotrophin releasing hormone analogues	
L02AE02	leuprorelin	8.3
L02B	*Hormone antagonists and related agents*	
L02BA	*Anti-estrogens*	
L02BA01	tamoxifen	8.3
L02BB	*Anti-androgens*	
L02BB03	bicalutamide	8.3
L02BG	*Aromatase inhibitors*	
L02BG03	anastrozole	8.3
L03	**Immunostimulants**	
L03A	Immunostimulants	
L03AA	*Colony stimulating factors*	
L03AA02	filgrastim	8.2
L03AB	Interferons	
L03AB10	peginterferon alfa-2b*	6.4.4.2.5
L03AB11	peginterferon alfa-2a*	6.4.4.2.5
L04	**Immunosuppressants**	
L04A	Immunosuppressants	
L04AD	*Calcineurin inhibitors*	

ATC code	ATC group/medicine or item	Section
L04AD01	ciclosporin	8.1
L04AX	*Other immunosuppressants*	
L04AX01	azathioprine	8.1; 30.2
M	**MUSCULO-SKELETAL SYSTEM**	
M01	**Antiinflammatory and antirheumatic products**	
M01A	Antiinflammatory and antirheumatic products, non-steroids	
M01AE	*Propionic acid derivatives*	
M01AE01	ibuprofen	2.1; 29
M01C	Specific antirheumatic agents	
M01CC	*Penicillamine and similar agents*	
M01CC01	penicillamine	4.2; 30.2
M03	**Muscle relaxants**	
M03A	Muscle relaxants, peripherally acting agents	
M03AB	*Choline derivatives*	
M03AB01	suxamethonium	20
M03AC	*Other quaternary ammonium compounds*	
M03AC03	vecuronium	20
M03AC04	atracurium	20
M04	**Antigout preparations**	
M04A	Antigout preparations	
M04AA	*Preparations inhibiting uric acid production*	
M04AA01	allopurinol	8.2; 30.1
M05	**Drugs for treatment of bone diseases**	
M05B	Drugs affecting bone structure and mineralization	
M05BA	*Bisphosphonates*	
M05BA08	zoledronic acid	8.2

ATC code	ATC group/medicine or item	Section
N	**NERVOUS SYSTEM**	
N01	**Anesthetics**	
N01A	Anesthetics, general	
N01AB	*Halogenated hydrocarbons*	
N01AB01	halothane	1.1.1
N01AB06	isoflurane	1.1.1
N01AX	*Other general anesthetics*	
N01AX03	ketamine	1.1.2
N01AX10	propofol	1.1.2
N01AX13	nitrous oxide	1.1.1
N01B	Anesthetics, local	
N01BB	*Amides*	
N01BB01	bupivacaine	1.2
N01BB02	lidocaine	1.2
N01BB52	lidocaine, combinations*	1.2
N02	**Analgesics**	
N02A	Opioids	
N02AA	*Natural opium alkaloids*	
N02AA01	morphine	1.3; 2.2
N02AA03	hydromorphone	2.2
N02AA05	oxycodone	2.2
N02AB	*Phenylpiperidine derivatives*	
N02AB03	fentanyl	2.2
N02B	*Other analgesics and antipyretics*	
N02BA	*Salicylic acid and derivatives*	
N02BA01	acetylsalicylic acid	2.1; 7.1
N02BE	*Anilides*	
N02BE01	paracetamol	2.1; 7.1
N03	**Antiepileptics**	
N03A	Antiepileptics	

ATC code	ATC group/medicine or item	Section
N03AA	*Barbiturates and derivatives*	
N03AA02	phenobarbital	5
N03AB	*Hydantoin derivatives*	
N03AB02	phenytoin	5
N03AD	*Succinimide derivatives*	
N03AD01	ethosuximide	5
N03AF	*Carboxamide derivatives*	
N03AF01	carbamazepine	5; 24.2.2
N03AG	*Fatty acid derivatives*	
N03AG01	valproic acid	5; 24.2.2
N03AX	*Other antiepileptics*	
N03AX09	lamotrigine	5
N04	**Anti-parkinson drugs**	
N04A	Anticholinergic agents	
N04AA	*Tertiary amines*	
N04AA02	biperiden	9
N04B	Dopaminergic agents	
N04BA	*Dopa and dopa derivatives*	
N04BA02	levodopa and decarboxylase inhibitor*	9
N05	**Psycholeptics**	
N05A	Antipsychotics	
N05AA	*Phenothiazines with aliphatic side-chain*	
N05AA01	chlorpromazine	24.1
N05AB	*Phenothiazines with piperazine structure*	
N05AB02	fluphenazine	24.1
N05AH	*Diazepines, oxazepines, thiazepines and oxepines*	
N05AH02	clozapine	24.1
N05AD	*Butyrophenone derivatives*	
N05AD01	haloperidol	2.3; 24.1
N05AN	*Lithium*	
N05AN01	lithium*	24.2.2

ATC code	ATC group/medicine or item	Section
N05AX	*Other antipsychotics*	
N05AX08	risperidone	24.1
N05B	Anxiolytics	
N05BA	*Benzodiazepine derivatives*	
N05BA01	diazepam	2.3; 5; 24.3
N05BA06	lorazepam	5
N05C	Hypnotics and sedatives	
N05CD	*Benzodiazepine derivatives*	
N05CD08	midazolam	1.3; 5
N06	**Psychoanaleptics**	
N06A	Antidepressants	
N06AA	*Non-selective monoamine reuptake inhibitors*	
N06AA04	clomipramine	24.4
N06AA09	amitriptyline	2.3; 24.2.1
N06AB	*Selective serotonin reuptake inhibitors*	
N06AB03	fluoxetine	24.2.1
N06B	Psychostimulants, agents used for ADHD and nootropics	
N06BC	*Xanthine derivatives*	
N06BC01	caffeine citrate	29
N07	**Other nervous system drugs**	
N07A	Parasympathomimetics	
N07AA	*Anticholinesterases*	
N07AA01	neostigmine	20
N07AA02	pyridostigmine	20
N07B	Drugs used in addictive disorders	
N07BA	*Drugs used in nicotine dependence*	
N07BA01	nicotine*	24.5
N07BC	*Drugs used in opioid dependence*	
N07BC02	methadone	2.2; 24.5

ATC code	ATC group/medicine or item	Section
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**	
P01	**Antiprotozoals**	
P01A	Agents against amoebiasis and other protozoal diseases	
P01AB	*Nitroimidazole derivatives*	
P01AB01	metronidazole	6.5.1
P01AC	*Dichloroacetamide derivatives*	
P01AC01	diloxanide	6.5.1
P01B	Antimalarials	
P01BA	*Aminoquinolines*	
P01BA01	chloroquine	2.4; 6.5.3.1; 6.5.3.2
P01BA02	hydroxychloroquine	30.2
P01BA03	primaquine	6.5.3.1
P01BA06	amodiaquine	6.5.3.1
P01BB	*Biguanides*	
P01BB01	proguanil	6.5.3.2
P01BC	*Methanolquinolines*	
P01BC01	quinine	6.5.3.1
P01BC02	mefloquine	6.5.3.1; 6.5.3.2
P01BD	*Diaminopyrimidines*	
P01BD01	pyrimethamine	6.5.4
P01BD51	pyrimethamine, combinations*	6.5.3.1
P01BE	*Artemisinin and derivatives*	
P01BE02	artemether	6.5.3.1
P01BE03	artesunate	6.5.3.1
P01BF01	artemether and lumefantrine	6.5.3.1
P01BF02	artesunate and mefloquine	6.5.3.1
P01BF03	artesunate and amodiaquine	6.5.3.1
P01BF05	artenimol and piperaquine	6.5.3.1
P01BF06	artesunate and pyronaridine	6.5.3.1
P01C	Agents against leishmaniasis and trypanosomiasis	
P01CA	*Nitroimidazole derivatives*	

ATC code	ATC group/medicine or item	Section
P01CA02	benznidazole	6.5.5.2
P01CB	*Antimony compounds*	
P01CB01	meglumine antimoniate	6.5.2
P01CB02	sodium stibogluconate	6.5.2
P01CC	*Nitrofuran derivatives*	
P01CC01	nifurtimox	6.5.5.1; 6.5.5.2
P01CD	*Arsenic compounds*	
P01CD01	melarsoprol	6.5.5.1
P01CX	*Other agents against leishmaniasis and trypanosomiasis*	
P01CX01	pentamidine isethionate*	6.5.4; 6.5.5.1
P01CX02	suramin sodium	6.5.5.1
P01CX03	eflornithine	6.5.5.1
P02	**Anthelmintics**	
P02B	Antitrematodals	
P02BA	*Quinoline derivatives and related substances*	
P02BA01	praziquantel	6.1.1; 6.1.3
P02BA02	oxamniquine	6.1.3
P02BX	*Other antitrematodal agents*	
P02BX04	triclabendazole	6.1.3
P02C	Antinematodal agents	
P02CA	*Benzimidazole derivatives*	
P02CA01	mebendazole	6.1.1
P02CA03	albendazole	6.1.1; 6.1.2
P02CB	*Piperazine and derivatives*	
P02CB02	diethylcarbamazine	6.1.2
P02CC	*Tetrahydropyrimidine derivatives*	
P02CC01	pyrantel	6.1.1
P02CE	*Imidazothiazole derivatives*	
P02CE01	levamisole	6.1.1
P02CF	*Avermectines*	

ATC code	ATC group/medicine or item	Section
P02CF01	ivermectin	6.1.1; 6.1.2
P02D	Anticestodals	
P02DA	*Salicylic acid derivatives*	
P02DA01	niclosamide	6.1.1
P03	**Ectoparasiticides, incl. scabicides, insecticides and repellents**	
P03A	Ectoparasiticides, incl. scabicides	
P03AC	*Pyrethrines, incl. synthetic compounds*	
P03AC04	permethrin	13.5
P03AX	*Other ectoparasiticides, incl. scabicides*	
P03AX01	benzyl benzoate	13.5
R	**RESPIRATORY SYSTEM**	
R01	**Nasal preparations**	
R01A	Decongestants and other nasal preparations for topical use	
R01AA	*Sympathomimetics, plain*	
R01AA07	xylometazoline	28
R01AD	*Corticosteroids*	
R01AD05	budesonide	28
R03	**Drugs for obstructive airway diseases**	
R03A	Adrenergics, inhalants	
R03AC	*Selective beta-2-adrenoreceptor agonists*	
R03AC02	salbutamol	25.1
R03AK	*Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics*	
R03AK07	formoterol and budesonide	25.1
R03B	Other drugs for obstructive airway diseases, inhalants	
R03BA	*Glucocorticoids*	
R03BA01	beclometasone	25.1

ATC code	ATC group/medicine or item	Section
R03BB	*Anticholinergics*	
R03BB01	ipratropium bromide	25.1
R03C	Adrenergics for systemic use	
R03CC	*Selective beta-2-adrenoreceptor agonists*	
R03CC02	salbutamol	25.1
R05	**Cough and cold preparations**	
R05D	Cough suppressants, excl. combinations with expectorants	
R05DA	*Opium alkaloids and derivatives*	
R05DA04	codeine	2.2
R06	**Antihistamines for systemic use**	
R06A	Antihistamines for systemic use	
R06AE	*Piperazine derivatives*	
R06AE3	cyclizine	2.3
R06AX	*Other antihistamines for systemic use*	
R06AX13	loratadine	3
R07	**Other respiratory system products**	
R07A	Other respiratory system products	
R07AA	*Lung surfactants*	29.1
S	**SENSORY ORGANS**	
S01	**Ophthalmologicals**	
S01A	Antiinfectives	
S01AA	*Antibiotics*	
S01AA09	tetracycline	21.1
S01AA10	natamycin	21.1
S01AA11	gentamicin	21.1
S01AA17	erythromycin	21.1
S01AD	*Antivirals*	

ATC code	ATC group/medicine or item	Section
S01AD03	aciclovir	21.1
S01B	Antiinflammatory agents	
S01BA	*Corticosteroids, plain*	
S01BA04	prednisolone	21.2
S01E	Antiglaucoma preparations and miotics	
S01EA	*Sympathomimetics in glaucoma therapy*	
S01EA01	epinephrine	21.5
S01EB	*Parasympathomimetics*	
S01EB01	pilocarpine	21.4
S01EC	*Carbonic anhydrase inhibitors*	
S01EC01	acetazolamide	21.4
S01ED	*Beta blocking agents*	
S01ED01	timolol	21.4
S01EE	*Prostaglandin analogues*	
S01EE01	latanoprost	21.4
S01F	Mydriatics and cycloplegics	
S01FA	*Anticholinergics*	
S01FA01	atropine	21.5
S01FA06	tropicamide	14.1
S01H	Local anesthetics	
S01HA	*Local anesthetics*	
S01HA03	tetracaine	21.3
S01J	Diagnostic agents	
S01JA	*Colouring agents*	
S01JA01	fluorescein	14.1
S02	**Otologicals**	
S02A	Antiinfectives	
S02AA	*Antiinfectives*	
S02AA10	acetic acid	28
S02AA15	ciprofloxacin	28

ATC code	ATC group/medicine or item	Section
V	**VARIOUS**	
V03	**All other therapeutic products**	
V03A	All other therapeutic products	
V03AB	*Antidotes*	
V03AB03	edetates*	4.2
V03AB06	thiosulfate*	4.2; 13.1
V03AB08	sodium nitrite	4.2
V03AB09	dimercaprol	4.2
V03AB14	protamine*	10.2
V03AB15	naloxone	4.2
V03AB17	methylthioninium chloride (methylene blue)	4.2
V03AB23	acetylcysteine	4.2
V03AB31	potassium ferric hexacyanoferrate (II) ·2H2O (Prussian blue)	4.2
V03AB34	fomepizole	4.2
V03AC	*Iron chelating agents*	
V03AC01	deferoxamine	4.2; 10.3
V03AF	*Detoxifying agents for antineoplastic treatment*	
V03AF01	mesna	8.2
V03AF03	calcium folinate	8.2
V03AN	*Medical gases*	
V03AN01	oxygen	1.1.1; 1.4
V04	**Diagnostic agents**	
V04C	Other diagnostic agents	
V04CF	*Tuberculosis diagnostics*	
V04CF01	tuberculin, purified protein derivative (PPD) - BCG*	19.1
V07	**All other non-therapeutic products**	
V07A	All other non-therapeutic products	
V07AB	*Solvents and diluting agents, incl. irrigating solutions**	26.3
V07AB	*Water for Injection*	26.3
V07AV	*Technical disinfectants**	15.2

ATC code	ATC group/medicine or item	Section
V08	**Contrast media**	
V08A	X-ray contrast media, iodinated	
V08AA	*Watersoluble, nephrotropic, high osmolar X-ray contrast media*	
V08AA01	diatrizoic acid*	14.2
V08AB	*Watersoluble, nephrotropic, low osmolar X-ray contrast media*	
V08AB02	iohexol	14.2
V08AC	*Watersoluble, hepatotropic X-ray contrast media*	
V08AC02	iotroxic acid*	14.2
V08B	X-ray contrast media, non-iodinated	
V08BA	*Barium sulfate containing X-ray contrast media*	
V08BA01	barium sulfate with suspending agents*	14.2

* Medicine or item name differs slightly from the name used.

Annex 4

Alphabetical list of essential medicines (with ATC classification code numbers)

Medicine or item as in EML	ATC code	Section
abacavir (ABC)	J05AF06	6.4.2.1
abacavir + lamivudine	J05AR02	6.4.2
acetazolamide	S01EC01	21.4
acetic acid	S02AA10	28
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	12.5.1
acetylsalicylic acid	N02BA01	2.1; 7.1; 30.3
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
albendazole	P02CA03	6.1.1; 6.1.2
allopurinol	M04AA01	8.2; 30.1
amikacin	J01GB06	6.2.2; 6.2.4
amiloride	C03DB01	16
amiodarone	C01BD01	12.2
amitriptyline	N06AA09	2.3; 24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amoxicillin	J01CA04	6.2.1
amoxicillin and enzyme inhibitor*	J01CR02	6.2.1
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
anastrozole	L02BG03	8.3
anti-D immunoglobulin	J06BB01	11.2.1
artemether	P01BE02	6.5.3.1
artemether and lumefantrine	P01BF01	6.5.3.1
artenimol and piperaquine	P01BF05	6.5.3.1
artesunate	P01BE03	6.5.3.1
artesunate a nd amodiaquine	P01BF03	6.5.3.1
artesunate and mefloquine	P01BF02	6.5.3.1
artesunate and pyronaridine	P01BF06	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2
atazanavir	J05AE08	6.4.2.3
atazanavir + ritonavir	J05ARxx	6.4.2.3
atenolol	C07AB03	12.3

Medicine or item as in EML	ATC code	Section
atracurium	M03AC04	20
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	8.1; 30.2
azithromycin	J01FA10	6.2.2; 21.1
aztreonam	J01DF01	6.2.1
bacterial and viral vaccines, combined*	J07CA	19.3
barium sulfate with suspending agents*	V08BA01	14.2
beclometasone	R03BA01	25.1
bedaquiline	J04AK05	6.2.4
bendamustine	L01AA09	8.2
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoyl peroxide	D10AE01	13.4
benzyl benzoate	P03AX01	13.5
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
bevacizumab	L01XC07	21.6
bicalutamide	L02BB03	8.3
biperiden	N04AA02	9
bisoprolol	C07AB07	12.1; 12.2; 12.3; 12.4
bleomycin	L01DC01	8.2
budesonide	R03BA02	25.1
budesonide	R01AD05	28
budesonide and formoterol	R03AK07	25.1
bupivacaine	N01BB01	1.2
caffeine citrate	N06BC01	29
calcium folinate	V03AF03	8.2
calcium gluconate	A12AA03	4.2; 27
capecitabine	L01BC06	8.2
capreomycin	J04AB30	6.2.4
carbamazepine	N03AF01	5; 24.2.2
carbamide*	D02AE01	13.4
carbohydrates*	B05BA03	26.2
carboplatin	L01XA02	8.2
carvedilol	C07AG02	12.1; 12.2; 12.3; 12.4
cefalexin	J01DB01	6.2.1
cefazolin	J01DB04	6.2.1

Medicine or item as in EML	ATC code	Section
cefepime	J01DE01	6.2.1
cefixime	J01DD08	6.2.1
cefotaxime	J01DD01	6.2.1
ceftaroline	J01DI02	6.2.1
ceftazidime	J01DD02	6.2.1
ceftriaxone	J01DD04	6.2.1
cephalosporins, fourth-generation	J01DE	6.2.1
chlorambucil	L01AA02	8.2
chloramphenicol	J01BA01	6.2.2
chlorhexidine	D08AC02	15.1; 29.1
chloroquine	P01BA01	6.5.3.1; 6.5.3.2; 30.2
chloroxylenol	D08AE05	15.2
chlorpromazine	N05AA01	24.1
cholera vaccines*	J07AE	19.3
ciclosporin	L04AD01	8.1
ciprofloxacin	J01MA02	6.2.2
ciprofloxacin	S02AA15	28
cisplatin	L01XA01	8.2
clarithromycin	J01FA09	6.2.2
clindamycin	J01FF01	6.2.2
clofazimine	J04BA01	6.2.3; 6.2.4
clomifene	G03GB02	18.6
clomipramine	N06AA04	24.4
clopidogrel	B01AC04	12.5.1
clotrimazole	G01AF02	6.3
cloxacillin	J01CF02	6.2.1
clozapine	N05AH02	24.1
coagulation factor IX, II, VII and X in combination*	B02BD01	11.2.2
coagulation factor VIII*	B02BD02	11.2.2
codeine	R05DA04	2.2
colecalciferol*	A11CC05	27
colistin	J01XB01	6.2.2
Combinations of drugs for treatment of tuberculosis*	J04AM	6.2.4
cyclizine	R06AE3	2.3
cyclophosphamide	L01AA01	8.2
cycloserine	J04AB01	6.2.4
cytarabine	L01BC01	8.2
dacarbazine	L01AX04	8.2
daclatasvir	J05AX14	6.4.4.2.3

Medicine or item as in EML	ATC code	Section
dactinomycin	L01DA01	8.2
dalteparin	B01AB04	10.2
dapsone	J04BA02	6.2.3
daptomycin	J01XX09	6.2.2
darbepoetin alfa	B03XA02	10.1
darunavir	J05AE10	6.4.2.3
dasabuvir	J05AX16	6.4.4.2.4
dasatinib	L01XE06	8.2
daunorubicin	L01DB02	8.2
deferoxamine	V03AC01	4.2; 10.3
delamanid	J04AK06	6.2.4
desmopressin	H01BA02	10.2
dexamethasone	H02AB02	2.3; 3; 8.3; 17.2; 29.2
dextran*	B05AA05	11.3
diatrizoic acid*	V08AA01	14.2
diazepam	N05BA01	2.3; 5; 24.3
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria toxoid*	J07AF01	19.3
docetaxel	L01CD02	8.2
docusate sodium	A06AA02	2.3
dolutegravir	J05AX12	6.4.2.4
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2
doxycycline	J01AA02	6.2.2; 6.5.3.1; 6.5.3.2
edetates*	V03AB03	4.2
efavirenz (EFV or EFZ)	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir disoproxil	J05AR06	6.4.2
efavirenz + lamivudine + tenofovir disoproxil	J05AR11	6.4.2
eflornithine	P01CX03	6.5.5.1
electrolytes with carbohydrates*	B05BB02	26.2
electrolytes*	B05BB01	26.2
emtricitabine + tenofovir disoproxil	J05AR03	6.4.2
enalapril	C09AA02	12.3; 12.4
encephalitis, Japanese, inactivated, whole virus*	J07BA02	19.3
encephalitis, tick-borne, inactivated, whole virus*	J07BA01	19.3

Medicine or item as in EML	ATC code	Section
enoxaparin	B01AB05	10.2
entecavir	J05AF10	6.4.4.1.1
ephedrine	C01CA26	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 12.2; 25.1
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.1
erythromycin	S01AA17	21.1
erythropoietin*	B03SA01	10.1
ethambutol	J04AK02	6.2.4
ethambutol and isoniazid	J04AM03	6.2.4
ethanol	D08AX08	15.1; 15.2
ethionamide	J04AD03	6.2.4
ethosuximide	N03AD01	5
etonorgestrel	G03AC08	18.3.5
etoposide	L01CB01	8.2
fentanyl	N02AB03	2.2
filgrastim	L03AA02	8.2
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fludarabine	L01BB05	8.2
fludrocortisone	H02AA02	18.1
fluorescein	S01JA01	14.1
fluorouracil	L01BC02	8.2; 13.4
fluoxetine	N06AB03	2.3; 24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
fomepizole	V03AB34	4.2
fosfomycin	J01XX01	6.2.2
fresh frozen plasma*	B05AX03	11.1
furosemide	C03CA01	12.4; 16
gemcitabine	L01BC05	8.2
gentamicin	J01GB03	6.2.2
gentamicin	S01AA11	21.1
glibenclamide	A10BB01	18.5
gliclazide	A10BB09	18.5
glucagon	H04AA01	18.5
glucose*	B05BA03	26.2

Medicine or item as in EML	ATC code	Section
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
haloperidol	N05AD01	2.3; 24.1
halothane	N01AB01	1.1.1
hemophilus influenzae B, purified antigen conjugated*	J07AG01	19.3
heparin*	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
hydrazaline	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.3; 18.1
hydromorphone	N02AA03	2.2
hydroxocobalamin	B03BA03	10.1
hydroxycarbamide	L01XX05	8.2; 10.3
hydroxychloroquine	P01BA02	30.2
hyoscine butylbromide*	A03BB01	2.3
hyoscine hydrobromide*	A04AD01	2.3
ibuprofen	M01AE01	2.1; 7.1; 29
ifosfamide	L01AA06	8.2
imatinib	L01XE01	8.2
immunoglobulins, normal human, for extravascular admin*	J06BA01	11.2.1
immunoglobulins, normal human, for intravascular admin*	J06BA02	11.2.1
influenza vaccine	J07BB	19.3
insulin injection (soluble)*	A10AB	18.5
insulin, intermediate-acting*	A10AC	18.5
Intravaginal contraceptives*	G02BB	18.3.4; 18.3.6
iodine*	D08AG03	6.3
Iodine therapy*	H03CA	18.8
iohexol	V08AB02	14.2
iotroxic acid*	V08AC02	14.2
ipratropium bromide	R03BB01	25.1
irinotecan	L01XX19	8.2
Iron in combination with folic acid*	B03AD	10.1
Iron preparations*	B03A	10.1

Medicine or item as in EML	ATC code	Section
isoflurane	N01AB06	1.1.1
isoniazid	J04AC01	6.2.4
isoniazid, combinations*	J04AC51	6.4.2.5
isopropanol*	D08AX05	15.2
isosorbide dinitrate	C01DA08	12.1
Isotonic solutions*	B05DA	23
itraconazole	J02AC02	6.3
ivermectin	P02CF01	6.1.1; 6.1.2
kanamycin	J01GB04	6.2.4
ketamine	N01AX03	1.1.2
lactulose	A06AD11	2.3
lamivudine (3TC)	J05AF05	6.4.2.1
lamivudine + nevirapine + zidovudine	J05AR05	6.4.2
lamivudine + zidovudine (ZDV or AZT)	J05AR01	6.4.2
lamotrigine	N03AX09	5
latanoprost	S01EE01	21.4
ledipasvir + sofosbuvir	J05AX65	6.4.4.2
leuprorelin	L02AE02	8.3
levamisole	P02CE01	6.1.1
levodopa and decarboxylase inhibitor*	N04BA02	9
levofloxacin	J01MA12	6.2.4
levonorgestrel	G03AC03	18.3.1; 18.3.3; 18.3.5
levonorgestrel	G03AD01	18.3.1
levonorgestrel and estrogen*	G03AB03	18.3.1
levonorgestrel and ethinylestradiol	G03AA07	18.3.1
levothyroxine sodium*	H03AA01	18.8
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine, combinations*	N01BB52	1.2
linezolid	J01XX08	6.2.2; 6.2.4
lithium*	N05AN01	24.2.2
loperamide	A07DA03	2.3
lopinavir + ritonavir (LPV/r)*	J05AR10	6.4.2.3
loratadine	R06AX13	3
losartan	C09CA01	12.3; 12.4
lorazepam	N05BA06	5
Lung surfactants	R07AA	29.1

Medicine or item as in EML	ATC code	Section
magnesium sulfate	B05XA05	5
mannitol	B05BC01	16
measles vaccine, live attenuated*	J07BD01	19.3
mebendazole	P02CA01	6.1.1
medicinal charcoal*	A07BA01	4.1
medroxyprogesterone and estrogen*	G03AA08	18.3.2
medroxyprogesterone*	G03AC06	18.3.2; 18.7
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
melarsoprol	P01CD01	6.5.5.1
meningococcal vaccines*	J07AH	19.3
mercaptopurine	L01BB02	8.2
meropenem	J01DH02	6.2.1
mesna	V03AF01	8.2
metformin	A10BA02	18.5
methadone	N07BC02	2.2; 24.5
methotrexate	L01BA01	8.2; 30.2
methoxy polyethylene glycol-epoetin beta	B03AX03	10.1
methyldopa (levorotatory)*	C02AB01	12.3
methylprednisolone	H02AB04	8.3
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	2.3; 17.2
metoprolol	C07AB02	12.1; 12.2; 12.3; 12.4
metronidazole	J01XD01	6.2.2
metronidazole	P01AB01	6.5.1
miconazole	D01AC02	13.1
midazolam	N05CD08	1.3; 2.3; 5
mifepristone	G03XB01	22.1
miltefosine	L01XX09	6.5.2
misoprostol	G02AD06	22.1
morphine	N02AA01	1.3; 2.2
moxifloxacin	J01MA14	6.2.4
multienzymes (lipase, protease, etc.)*	A09AA02	17
mumps vaccine, live attenuated*	J07BE01	19.3
mupirocin	D06AX09	13.2
nadroparin	B01AB06	10.2
naloxone	V03AB15	4.2
natamycin	S01AA10	21.1
neostigmine	N07AA01	20

Medicine or item as in EML	ATC code	Section
nevirapine (NVP)	J05AG01	6.4.2.2
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27
nicotine*	N07BA01	24.5
nifedipine	C08CA05	22.2
nifurtimox	P01CC01	6.5.5.1; 6.5.5.2
nilotinib	L01XE08	8.2
nitrofurantoin	J01XE01	6.2.2
nitroprusside*	C02DD01	12.3
nitrous oxide	N01AX13	1.1.1
norethisterone and ethinylestradiol	G03AA05	18.3.1
norethisterone*	G03AC01	18.3.2
nystatin	D01AA01	6.3
ofloxacin	S01AE01	21.1
ombitasvir + paritaprevir + ritonavir	J05AX66	6.4.4.2
omeprazole	A02BC01	17.1
ondansetron	A04AA01	2.3; 17.2
oral rehydration salt formulations*	A07CA	17.5.1; 26.1
oseltamivir	J05AH02	6.4.3
other antiseptics and disinfectants*	D08AX	15.2
other cephalosporins and penems	J01DI	6.2.1
other mineral products*	A12CX	27
oxaliplatin	L01XA03	8.2
oxamniquine	P02BA02	6.1.3
oxycodone	N02AA05	2.2
oxygen	V03AN01	1.1.1; 1.4
oxytocin	H01BB02	22.1
paclitaxel	L01CD01	8.2
p-aminosalicylic acid*	J04AA01	6.2.4
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
peginterferon alfa-2a*	L03AB11	6.4.4.2.5
peginterferon alfa-2b*	L03AB10	6.4.4.2.5
penicillamine	M01CC01	4.2; 30.2
pentamidine isethionate*	P01CX01	6.5.4; 6.5.5.1
permethrin	P03AC04	13.5
pertussis vaccine	J07AJ01	19.3
phenobarbital	N03AA02	5

Medicine or item as in EML	ATC code	Section
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
piperacillin and enzyme inhibitor*	J01CR05	6.2.1
plastic IUD with copper*	G02BA02	18.3.3
plastic IUD with progesteron*	G02BA03	18.3.3
platelet concentrates	B05A	11.1
pneumococcus, purified polysaccharides antigen*	J07AL01	19.3
podophyllotoxin*	D06BB04	13.4
poliomyelitis vaccine	J07BF	19.3
polymyxins	J01XB	6.2.2
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II) ·2H2O (Prussian blue)	V03AB31	4.2
potassium permanganate	D08AX06	13.2
povidone-iodine*	D08AG02	15.1
praziquantel	P02BA01	6.1.1; 6.1.3
prednisolone	H02AB06	3; 8.3
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1
procaine benzylpenicillin	J01CE09	6.2.1
procarbazine	L01XB01	8.2
progesterone	G03DA04	18.3.6
proguanil	P01BB01	6.5.3.2
propofol	N01AX10	1.1.2
propranolol	C07AA05	7.2
propylthiouracil	H03BA02	18.8
prostaglandins*	C01EA	29.1
protamine*	V03AB14	10.2
protionamide	J04AD01	6.2.4
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.4
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
pyrimethamine, combinations*	P01BD51	6.5.3.1
quinine	P01BC01	6.5.3.1

Medicine or item as in EML	ATC code	Section
rabies immunoglobulin	J06BB05	11.2.1
rabies vaccine	J07BG	19.3
raltegravir	J05AX08	6.4.2.4
ranitidine	A02BA02	17.1
red blood cells*	B05AX01	11.1
retinol	A11CA01	27
ribavirin	J05AB04	6.4.3; 6.4.4.2.5
riboflavin	A11HA04	27
rifabutin	J04AB04	6.2.4
rifampicin	J04AB02	6.2.3; 6.2.4
rifampicin and isoniazid*	J04AM02	6.2.4
rifampicin, pyrazinamide and isoniazid*	J04AM05	6.2.4
rifampicin, pyrazinamide, ethambutol and isoniazid*	J04AM06	6.2.4
rifapentine	J04AB05	6.2.4
risperidone	N05AX08	24.1
ritonavir (r)	J05AE03	6.4.2.3
rituximab	L01XC02	8.2
rota virus diarrhea vaccines*	J07BH	19.3
rubella vaccines	J07BJ	19.3
salbutamol	R03CC02	25.1
salicylic acid	D01AE12	13.4
selenium sulfide	D01AE13	13.1
senna glycosides*	A06AB06	2.3; 17.4
silver sulfadiazine	D06BA01	13.2
simeprevir	J05AE14	6.4.4.2.2
simvastatin	C10AA01	12.6
snake venom antiserum*	J06AA03	19.2
sodium bicarbonate*	B05XA02	26.2
sodium chloride	B05XA03	26.2
sodium fluoride	A12CD01	27
sodium nitrite	V03AB08	4.2
sodium stibogluconate	P01CB02	6.5.2
sofosbuvir	J05AX15	6.4.4.2.1
sofosbuvir + velpatasvir	J05AX69	6.4.4.2
Solvents and diluting agents, incl. irrigating solutions*	V07AB	26.3
spectinomycin	J01XX04	6.2.2
spironolactone	C03DA01	12.4; 16
streptokinase	B01AD01	12.5.2
streptomycin	J01GA01	6.2.4

Medicine or item as in EML	ATC code	Section
sulfadiazine	J01EC02	6.5.4
sulfamethoxazole + trimethoprim	J01EE01	6.2.2; 6.5.4
sulfasalazine	A07EC01	17.3; 30.2
suramin sodium	P01CX02	6.5.5.1
suxamethonium	M03AB01	20
tamoxifen	L02BA01	8.3
tars*	D05AA	13.4
Technical disinfectants*	V07AV	15.2
tenofovir disoproxil fumarate	J05AF07	6.4.2.1; 6.4.4.1.1
terbinafine	D01BA02	13.1
terizidone	J04AK03	6.2.4
testosterone	G03BA03	18.2
tetanus immunoglobulin*	J06BB02	11.2.1
tetanus toxoid*	J07AM01	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thiamine	A11DA01	27
thiosulfate*	V03AB06	4.2; 13.1
tigecycline	J01AA12	6.2.2
timolol	S01ED01	21.4
tioguanine	L01BB03	8.2
tranexamic acid	B02AA02	10.2
trastuzumab	L01XC03	8.2
tretinoin*	L01XX14	8.2
triclabendazole	P02BX04	6.1.3
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD) - BCG*	V04CF01	19.1
tuberculosis, live attenuated*	J07AN01	19.3
typhoid vaccine	J07AP	19.3
ulipristal	G03AD02	18.3.1
valganciclovir	J05AB14	6.4.3
valproic acid	N03AG01	5; 24.2.2
vancomycin	J01XA01	6.2.2
varicella zoster vaccines*	J07BK	19.3
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2
vinblastine	L01CA01	8.2

Medicine or item as in EML	ATC code	Section
vincristine	L01CA02	8.2
vinorelbine	L01CA04	8.2
voriconazole	J02AC03	6.3
warfarin	B01AA03	10.2
Water for Injection	V07AB	26.3
whole blood*	B05A	11.1
xylometazoline	R01AA07	28
yellow fever vaccines	J07BL	19.3
zidovudine (ZDV or AZT)	J05AF01	6.4.2.1
Zinc products*	D02AB	13.3
zinc sulfate	A12CB01	17.5.2
zoledronic acid	M05BA08	8.2

* Medicine or item name differs slightly from the name used.

This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model Lists of Essential Medicines. It contains a summary of the Committee's considerations and justifications for additions and changes to the Model Lists, including its recommendations. Annexes to the main report include the revised version of the WHO Model List of Essential Medicines (20th edition) and the WHO Model List of Essential Medicines for Children (6th edition). In addition there is a list of all the items on the Model Lists sorted according to their Anatomical Therapeutic Chemical (ATC) classification codes.

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