WHO Technical Report Series

The Selection and Use of Essential Medicines

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

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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, extend the indications for 6 existing listed medicines, 5 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 adding additional indications for 9 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 empiric 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.

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

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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 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 addition of a new indication for methadone for management 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 that this product is a sub-optimal treatment for cancer pain compared to morphine and other strong opioids.

Section 6.2: Antibacterials

Section 6 of the Essential Medicines List covers anti-infective medicines. Disease-specific sub-sections within Section 6 of the EML 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) have not been similarly reviewed and updated and so were the focus of a comprehensive review in 2017. This revision addresses Objective 4 of the WHO's Global Action Plan on Antimicrobial Resistance 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 multi-drug 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, but the Committee did not change antibiotic listings in Section 6.4.2 Antituberculosis medicines as a result of this review.

Having considered the proposals put forward for its consideration, the Expert Committee decided to only consider treatments for common infectious syndromes, excluding rare or hospital-acquired infections. The Committee then identified empiric treatment choices for common, community-acquired infections that are broadly applicable in the majority of countries, using parsimony as a guiding principle. Alternative options for patients with allergy to specific products were not considered. The Committee

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recommended first and second choice antibiotics for each syndrome. First and second choice antibiotics 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 groups.

The Committee specifically noted that the evidence base for recommending specific antibiotics and classes into the different categories was weak and the List will need further revision over time as new evidence is identified. It was also clearly recognized that the general principles of Access/Watch/Reserve apply to many other antimicrobials, including antituberculosis, antimalarial, antivirals, antifungals and others.

The groups are described and defined in detail below.

ACCESS GROUP

This group includes antibiotics recommended as empiric, 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 cost, in appropriate formulations and of assured quality. First choices are usually narrow spectrum agents with positive benefit-to-risk ratios, and low resistance potential, whereas second choices are generally broader spectrum antibiotics with higher resistance potential, or less favorable benefit-to-risk 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 be listed in the WATCH group as well. Their use should be limited and monitored.

Access group antibiotics			
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

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WATCH GROUP

This 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 programs and monitoring. This group includes the highest priority agents on the list of Critically Important Antimicrobials (CIA) for Human Medicine[2]. 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
Anti-pseudomonal penicillins with beta-lactamase inhibitor e.g. piperacillin + tazobactam
Carbapenems e.g. meropenem, imipenem + cilastatin
Penems e.g. faropenem

RESERVE GROUP

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

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

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Reserve group ('last-resort') 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

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 or work on the current clinical synopsis reviews 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 for EML/c;
- review the differential effect of antibiotic classes on the selection of resistance;
- relate the work of the EML/c 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 programs.

Section 6.2.4: Antituberculosis medicines

The Expert Committee recommended the listing of clofazimine for the new indication of multi-drug resistant tuberculosis (MDR-TB) on the complementary list of the EML and EMLc. The Expert Committee also recommended the addition of delamanid to the complementary list of the EMLc for the treatment of MDR-TB in children aged 6 to 17 years. Two paediatric fixed-dose combination formulations of isoniazid, pyrazinamide and rifampicin, and isoniazid and 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 to harm ratio compared with 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, was made into 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.

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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 the addition 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 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 compared to when oseltamivir was first included on the Model List in 2009, there now exists additional evidence of oseltamivir in seasonal and pandemic flu which has reduced the previously estimated magnitude of effect of oseltamivir on relevant clinical outcomes. The Committee recommended the listing of oseltamivir be amended and the medicine be moved from the core to the complementary list, and its use be restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients. The Expert EML Committee noted that WHO guidelines for pharmacological management of pandemic and seasonal influenza are going to be updated in 2017: unless new information supporting the use in seasonal and pandemic outbreaks is provided, 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 Expert Committee did not recommend listing for other proposed cancer medicines: enzalutamide for metastatic breast 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

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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 the single medicines given concomitantly, including increased 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, 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 to make choices for national EML selection.

Section 18: Hormones, Other Endocrine Medicines & 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 to 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 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 indicated above, the Expert Committee did not recommend the addition of ready to use therapeutic food (RUTF) or hypochlorous acid solution. The Committee did not recommend deletion of bevacizumab for ocular indications, nor deletion of the indication of prevention of post-partum haemorrhage from the listing for misoprostol.

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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 as this 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 was discussed, notably for those for cancer and diabetes.

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/

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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
Itraconazole	Fungal infection	Lamotrigine	Epilepsy
Lamotrigine	Epilepsy	*Methadone*	Cancer pain
Losartan	Hypertension	*Meropenem*	Antibiotic
Meropenem	Antibiotic	Natamycin	Fungal infection
Natamycin	Fungal infection	*Oxazolindinones*	Reserve antibiotics
Nilotinib	Chronic myeloid leukaemia	Piperacillin + tazobactam	Antibiotic
Oxazolindinones	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		

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Ulipristal	Emergency contraception	
Voriconazole	Fungal infection	
Zoledronic acid	Bone metastases	

EML - New / changed indications		**EMLc - New /changed indications**	
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		

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

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EML - Medicines / formulations deleted		**EMLc - Medicines / formulations deleted**	
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	Nevirapine	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		

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List of participants

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Temporary advisers

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Wilma Doedens, UNFPA Office in Geneva

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WHO Regions

WHO Regional Office for the Americas / Pan American Health Organization

Jose Luis Castro, Advisor, Rational Use of Medicines, Washington DC, United States of America

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Observers

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WHO Secretariat

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

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

Nicola Magrini, 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, EML Secretariat; Innovation, Access and Use, Department of Essential Medicines and Health Products.

Bernadette Cappello, Technical Officer, EML Secretariat; 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.

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Declaration of Interests for Expert Committee Members, Temporary Advisers and WHO Secretariat

Declarations of interests of Expert Committee Members and Temporary Advisers

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 Essential Medicines and Health Products Department sought the advice of the Office of Compliance, Risk Management and Ethics.

Over 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.

Prior to the Expert Committee meeting, all Members and Temporary Advisers of the 21st Expert Committee on the Selection and Use of Essential Medicines submitted written disclosures of competing interests that were relevant for consideration prior to confirmation as members of the said meeting. These 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; whether the institution or employer has a financial relationship with 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: this included leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about a medicine. In addition, at the start of the Expert Committee, all members were asked to update their declaration if any new conflicts may have originated in the meantime.

Members and Temporary Advisers who did declare to not have financial conflicts of interests were: Lisa Bero, Zeba Aziz, Facundo Garcia-Bournissen, Sumanth Gandra, Mohammed Hassar, Robert Mvungi, Francis Ofei, Gabriela Prutsky-Lopez, Shalini Sri Ranaganathan, Fatima Suleman, Worasuda Yoongthong and Mei Zeng.

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

Dr Franco Cavalli declared that his institution (Ente Ospedaliero Cantonale, Switzerland) has received funding from Mundipharma for testing a medicine in testicular

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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.

Dr Graham Cooke declared that his institution (Imperial College London, UK) 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 Janssen, Bristol-Myers Squibb and Gilead. Dr Cooke declared that he is chairing the Lancet Commission on Hepatitis C, for which he is unpaid.

Dr Stephan Harbarth is leading the WHO Collaborating Centre on Patient Safety Infection Control Program. Dr Harbarth 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. Dr Harbarth 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 under evaluation at this meeting.

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

Dr 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).

Dr Celine Pulcini declared that her institution (University of Lorraine, France) has received funding from the Innovative Medicines Initiative, a joint undertaking between the European Union and the European Pharmaceutical Industry Association (EFPIA), to participate in the DRIVE-AB (Driving reinvestment in research and development and responsible antibiotic use) Project (Workpackage 1a). This project is not related to antibiotics under evaluation at this meeting.

Dr 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 London), is involved in multicentred trials as one site to test the efficacy of vaccines and antibiotics in children receiving institutional funding from GSK, Pfizer, Medimmune, Janssen, Novartis, Novovax, Regeneron, Ablynx, Alios, Cubist and Cempra.

After analysing each DOI, 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

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process. Conflicts of interests declared by Dr Gregory Kearns were considered minor. No other member had personal financial or commercial interests related to medicines under evaluation. Institutional grants and funding were considered not creating the potential for inappropriate influence over the Expert Committee members and Temporary Advisers. Therefore, options for conditional participation, partial or total exclusion of any expert were 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.

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

In 2014 Dr 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 (bevacizumab) under evaluation. While it was determined that Dr Magrini did not have any direct conflict of interest with respect to the evaluation of bevacizumab, he was advised he might consider, of his own volition, recusing himself from this part of the evaluation in order to avoid a perceived conflict of interest. Nicola Magrini did decide to recuse himself from participating in the discussions and formulation of the recommendation on bevacizumab.

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1. Introduction

The 21st meeting of the World Health Organization (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, Health Systems and Innovation.

Dr Hill welcomed committee members and temporary advisers, representatives from WHO regional offices, non-governmental organizations and other participants on behalf of the Director-General.

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

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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 non-governmental 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 EML later in 2017 and recognized the Model List as one of the flagship products of the Organization. Dr Kieny summarised some historical achievements over 40 years of the EML and its evolution over time, stressing the importance of transparency and rigorous evaluation of evidence supporting both the efficacy estimates of medicines and their benefit to risk 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 and not as representatives of their governments or organizations, and of their responsibility 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 Advisor, 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, Medicins Sans Frontières (MSF)
- Brendan Shaw, International Federation of Pharmaceutical Manufactures & Associates (IFPMA)
- Esteban Burrone, Medicines Patent Pool (MPP)
- Thiru Balasubramanian, Knowledge Ecology International (KEI)

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- Margaret Ewen, Health Action International (HAI)
- Manica Balasegaram, (DNDI-GARDP)

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

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3. General items

Alignment between the Essential Medicines List and WHO guidelines

With the introduction of GRADE methodology 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 has been important investments in terms of evidence synthesis and improvements in guideline reporting.

In some therapeutic areas, WHO guidelines are frequently and regularly updated (HIV, Hepatitis B and C, tuberculosis, malaria, some priority neglected tropical diseases, contraception and family planning, sexually transmitted infections) with the use of fully updated systematic reviews and/or network meta-analyses that can form the basis for an optimal decision-making process and also for informing decisions regarding medicines for EML listing. When these high quality evidence summaries based on fully updated systematic reviews are available, these are shared with the EML Secretariat to coordinate WHO policy actions and improve consistency and alignment. There has been increasing attention to share with WHO Guidelines Steering Groups approaches and evidence summaries from the planning stage to better coordinate EML applications and their evaluation. Timing of publication of both WHO guidelines and EML has also been co-ordinated to minimize inconsistencies and unintended delays.

New format for the Technical Report Series (TRS)

In an effort to ensure that the Technical Report Series (TRS) chapters represent the best evidence currently available and can better inform country policies, the format of each medicines chapter or section has been revised. A new format for reporting information on medicines has been developed: this structured reporting has several advantages for readers, as it assists health professionals and policy makers in identifying basic information such as the ATC code or key findings such as the magnitude of benefits and harms associated with the medicine and additional evidence (not in the application) considered by the Expert Committee. The 2017 TRS uses the new reporting standard 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 has steadily increased, the structured format aids more rapid y retrieval of the relevant information during the decision-making process of the Expert Committee and for readers. At the same time, there is increasing awareness that health professionals and policy makers need succinct, structured and uniform summaries to understand the key findings on medicines and to facilitate judgments on the public health relevance of an application for countries. The number of medicines evaluated as part of comprehensive review of syndromes as opposed to applications targeting medicines individually is increasing: examples are antibiotic and diabetes medicines reviews this year and cancer medicines, as a continuation of what was done in 2015. This comprehensive approach allows a comparative evaluation among all available therapeutic options for target diseases or a specific indication, facilitating or actually allowing for broader comparisons and more selective listing.

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Increasing affordability of high priced medicines

The issue of affordability was raised when discussing a number of high-priced medicines, specifically those for cancer, hepatitis C and diabetes. 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 to make them more affordable and widely accessible. The Committee highlighted the need for ongoing assessment at country level of pricing mechanisms, availability and access issues of high priced medicines that are added to the EML and/or EMLc.

EML Working Groups and comprehensive reviews

The Expert Committee recommended the establishment of three standing Working Groups to prepare the work for next Expert Committee 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 trials results.

An EML Antibiotics Working Group should be established with the task of continuing the work initiated with the 2017 comprehensive review of the antibiotic section and to prepare the work of next Expert Committee. Specifically, the Committee recommended review of additional infectious disease syndromes, including typhoid fever, medical and surgical prophylaxis, dental infections, acute undifferentiated fever and other globally relevant ones. The EML Antibiotics Working Group could revise and consolidate the newly proposed categorization antibiotics ("Access", "Watch" and "Reserve" Groups), assessing if this tool can assist in activities such as local, national and global monitoring of antibiotic use, development of guidelines and educational activities to improve antibiotics use. Changes to the existing listings and groupings over time are possible, with the aim of balancing 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 in order to be more explicit on the principles guiding the selection of optimal medicines to be considered for EML inclusion and review available tools and thresholds for clinical and public health relevance of a medicine. There is also a need to improve application quality and have more comprehensive comparative evaluations 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 oncology conditions for review that were not part of the previous update, including (but not limited to) multiple myeloma, renal and brain cancers.

Finally, the Committee recognized the impact that selective reporting and publication bias can have on the availability of data for applications for 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. The Committee proposed a Working Group be established 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

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closely with the Department of Information, Evidence and Research on full and timely public disclosure of results from clinical trials.

Proposal for a WHO list of essential in vitro diagnostics

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

- The Committee acknowledged that diagnostic tests are essential to diagnose the disease or subpopulation for which certain medicines may be indicated, and to monitor the medication effectiveness or toxicity. Furthermore, often the diagnosis has important implications for prognosis.
- The Committee recognized that Member States and countries might seek advice about which 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 recognised that the idea of having a Model List of Essential In Vitro Diagnostics developed and maintained by WHO merits exploring, using the Model List of Essential Medicines as a "model" for its process, methodology and transparency.
- The diagnostics list may initially focus on in vitro diagnostics."
- The initial proposed priority areas (TB, malaria, HIV and Hepatitis B & C) may be appropriate for the first iteration of the list but should expand to other areas including other antimicrobials and non-communicable diseases as soon as possible.
- The Committee recommended that strong links should be maintained between the SAGE-IVD committee that is planned to oversee the diagnostics list and the Expert Committee on Selection and Use of Essential Medicines.
- The diagnostics list should be instrumental in developing medical guidelines as well as laboratory-accreditation schemes.

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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), oxazolindinones, 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 multi-drug resistant tuberculosis (MDR-TB) in children aged 6 years an older. 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 sub-section (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 sub-section (6.4.2.5) for mediciens 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), darbepoietin alfa, methoxy polyethylene glycol-epoietin beta (EML) and epoetin (alfa, beta, theta), darbepoietin alfa (EMLc) and their respective biosimilars.

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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 representatives of the pharmacological classes of inhaled corticosteroids (ICS) and long-acting beta-agonists, was added to the core list of the EML for the management of asthma as regular maintenance therapy. The product was not added to the EMLc due to safety concerns of high doses of ICS in children.

Deletions from Model Lists

Section 6.2.4: Ofloxacin, as an alternative to levofloxacin for MDR-TB, was deleted from the EML and EMLc. Streptomycin was removed from the core list of the EML as a first-line TB 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 of suspected influenza infection in critically ill hospitalized patients.

New indications

Section 1.4 (new sub-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 sub-section "1.4 Medical gases". The title of the full section 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.

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Section 6.1: an additional indication for ivermectin for use as an intestinal helminthic 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 both lists.

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 multi-drug 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/5mL) was added to the core list of the EML and EMLc. It was also added to Section 7.1 (anti-migraine medicines).

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

Section 6.4.2: A new strength of abavacir+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 sub-optimal cancer pain treatment compared to 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 multi-drug resistant tuberculosis was not recommended, as the available evidence did not show gatifloxacin to have a superior benefit to harm ratio compared to alternative fluoroquinolones included on the list.

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

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

Section 6.4.4: The application for addition of tenofovir alafenanmide to the core list of the EML for treatment of chronic hepatitis B was not recommended on limited evidence of a relevant clinical advantage over. 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 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 chlice from the variety of combinations, components and dosages required to appropriately taylor therapy. Explanatory text was added to this section of the list recognizing the potential value of FDCs of currently listed essential medicines in increasing 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 as a wound disinfectant and in wound management was not recommended on the basis 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 on the basis of higher cost outweighing potential benefits compared with human insulin. The application proposing addition of various second-line treatments for type 2 diabetes was not recommended, on the basis 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, and 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 post-partum haemorrhage from the listing for misoprostol on the EML was rejected. There was insufficient new clinical

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data included in the application for the Committee to change the circumstances of use 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 due to uncertain potential implications of listing RUTF on the EML in terms of availability of alternatives, different manufacturing standards for foods and pharmaceuticals, cost and access.

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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 sub-section)

Oxygen

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:	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:	New sub-section: 1.4 Medical gases
Dose form(s) & strengths(s):	Inhalation (medical gas)
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: **(if relevant, eg. resubmission, previous EC consideration)**	Oxygen has been included on the EML since 1979 and on the EMLc since its inception in 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 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% CI 3.93 to 7.63). Similarly, an increased risk of death was observed in meta-analysis of 3 studies involving 673 children with SpO2 less than 92% (OR 3.66, 95% CI 1.42 to 9.47) (10).

Summary of evidence: harms (from the application)	Hyperoxia, excess supply or concentration of oxygen to 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 necessary to balance risks of oxygen toxicity against risks associated with targeting lower oxygen saturations including neurological damage and death, and optimise 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 305 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):

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	– 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, if available, oxygen should be administered by a device that controls concentration to 24% to 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 which concentrate oxygen from ambient air), the estimated cost per 1000 L is US$2-8. The estimated cost from pipeline systems was not available. Total costs for oxygen supply will vary based on the options for static or consumable sources, training and maintenance and other associated costs.
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 sub-section "1.4 Medical gases". In addition, the Committee considered that the current overall section title of "Anaesthetics" is not truly representative of the medicines listed in the sub-sections, so recommended that Section 1 be re-titled "Anaesthetics, preoperative medicines and medical gases". The 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 Expert Committee accepted that there are ethical issues associated with conducting randomized controlled trials 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 hypoxemic patients with oxygen. The important role 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 its inclusion on the EML and EMLc for the new indication could be a factor contributing to improve the current situation, alongside other actions.

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Section 2: MEDICINES FOR PAIN AND PALLIATIVE CARE

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

Paracetamol – addition of 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:	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) & strengths(s):	Oral liquid: 120 mg /5 mL
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Paracetamol oral liquid 125 mg/5mL 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.
Availability:	UNICEF advised that when procuring paracetamol oral liquid, it procures the product listed on the EML and EMLc (which is oral liquid 125mg/5 mL). It states that the majority of suppliers from which they procure paracetamol oral liquid offer the alternative strength of 120mg/5 mL. It proposes 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 to the EML and EMLc, noting its wider global market availability than the currently listed 125mg / 5mL 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.

References: Nil.

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2.2 Opioid analgesics

Fentanyl (addition) – EML

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:	Dr Carla Ripamonti, Fondazione IRCCS, Instituto Nazionale Tumori, Milan, Italy and Dr Raffaele Giusti, Medical Oncology Unit, Sant'Andrea Hospital,Rome, Italy
WHO Technical Department:	WHO Department of Mental Health and Substance Abuse
EML / EMLc	EML and EMLc
Section:	2.2. Opioid Analgesics
Dose form(s) & strengths(s):	The application did not specify the dose forms and strengths proposed for inclusion. The following dose forms and strengths are available: Transdermal patch: 12, 25, 50,75 and 100 micrograms/hour
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 cancer symptom which occurs 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, with 70% of deaths from cancer occurring in low- and middle-income countries (LMICs). 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 fentanyl as a treatment alternative to morphine for use in cancer pain in order to help increase access to opioid pain relief for cancer patients.

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Summary of evidence: benefits (from the application)	Fentanyl is a potent synthetic opioid that is suitable for transdermal administration that 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 (eg, due to malabsorption, dysphagia vomiting or severe constipation) (5) and in patients with renal impairment. The application presented the findings of a literature search of papers published since 2012 of transdermal fentanyl and cancer pain. Only one randomized trial was identified, that compared transdermal fentanyl and pregabalin for neuropathic cancer pain (6). A 2013 Cochrane systematic review of nine trials involving 1,244 patients assessed the analgesic efficacy and adverse events of transdermal fentanyl for moderate to severe cancer pain cancer pain (7). The quality of evidence in the included studies was limited, with small numbers and failure to report clinically relevant outcomes. However, based on the findings of the review, the authors concluded that for patients able to tolerate treatment and remain in the study until its end, 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 to 0.78). A systematic review by Koyyalagunta et al (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 to 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, somnolence. Rash, application site reactions, itch have also been reported with the transdermal formulation (5). Transdermal fentanyl may cause less constipation than oral morphine (7). Case reports of severe diarrhoea associated with transdermal fentanyl during the first 72 hours of treatment have been reported (11).
Additional evidence: (not in the application)	van Seventer et al. (12) compared transdermal fentanyl and sustained-release oral morphine in opioid-naïve patients with moderate-to-severe cancer pain and in opioid-experienced patients with mild-to-moderate pain. 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. The authors concluded that transdermal fentanyl is as effective 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, nor 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 drug remaining in used transdermal patches after 72 hours has been reported to be between 28% and 84.4% (14, 15). There is potential for harms, misuse and abuse associated with residual fentanyl in used patches and appropriate, safe disposal of used patches is necessary.
WHO Guidelines:	The WHO Guidelines for Management of Cancer Pain are currently under review.

	2012 WHO 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 with medical illnesses (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 the route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, low quality evidence). Alternative opioids to morphine included in the guidelines include fentanyl, hydromorphone, methadone and oxycodone. Administration by the oral route is recommended.
Costs / cost-effectiveness:	No information regarding costs or cost-effectiveness is provided in the application. De Lima et al (17) studied the global availability and prices of opioids in a cross-sectional study. Oral methadone was found to be the least expensive of the five opioids studied (morphine, methadone, fentanyl, hydromorphone and oxycodone) with a median price for 30-days of treatment of US$ 0.5. Transdermal fentanyl had a median price for 30 days of treatment of US$ 2.2 In comparison, the median price for 30-days treatment of immediate release oral morphine tablet/capsule 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 a new cancer pain guideline that is 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 for treatment of cancer pain. 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 to the EMLc due adverse events and concern regarding over-dosing. The Committee noted there is potential for harms, misuse and abuse associated with residual fentanyl in used patches and appropriate, and that safe disposal of used patches is necessary.

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Methadone (new indication) EML and (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:	Dr Carla Ripamonti, Fondazione IRCCS, Instituto Nazionale Tumori, Milan, Italy and Dr Raffaele Giusti, Medical Oncology Unit, SantÁndrea Hospital of Rome, Italy
WHO Technical Department:	WHO Department of Mental Health and Substance Abuse
EML / EMLc	EML & EMLc
Section:	2.2. Opioid Analgesics
Dose form(s) & strengths(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: 1mg/mL, 2mg/mL, (as hydrochloride) Oral concentrate: 5mg/mL, 10mg/mL (as hydrochloride)
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 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 cancer symptom which occurs 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, with 70% of deaths from cancer occurring in low- and middle-income countries (LMICs). 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 for use in cancer pain in order to help increase access to opioid pain relief for cancer patients.

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Summary of evidence: benefits (from the application)	Analgesic treatment guidelines often consider morphine and other opioids comparable and interchangeable in the treatment of chronic cancer pain, but individual responses to these medicines may vary. A study comparing 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- or poor-responders. In addition, all patients required continuous dose adjustments to experience good analgesic response and patients treated with morphine often required switching to alternative opioids. Adverse effects are similar, with the exception of CNS effects, which were found to occur more commonly with morphine (5). Compared to morphine, methadone has similar affinity to mu- and kappa-opioid receptors and greater affinity for delta-opioid receptors (6, 7). Unlike morphine, methadone also blocks NMDA receptors, inhibits neuronal serotonin and norephinephrine reuptake, thereby inhibiting nociceptive transmission (8, 9). The analgesic effect of methadone is probably mediated by synergistic mechanisms that are different to 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. Methadone is primarily metabolised in the liver to inactive metabolites whereas morphine is primarily metabolised 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 literature search of papers published since 2012 of 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 experiencing neuropathic pain and who were naive to strong opioids (11). In addition, a series of systematic reviews were identified (published between 2012 and 2016) that investigated methadone for cancer in various circumstances including patients receiving methadone maintenance therapy for opioid addiction, methods of rotation from other opioids, and use in the elderly. Most of the systematic reviews identified determined the level of evidence to be low. In the systematic review by Good et al of RCTs of methadone in cancer pain published post-2007, the authors concluded that due to differences in methodology and study design, no definite conclusion could be made regarding the efficacy, safety or rotation strategies of 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. The retrospective study by Peirano et al (13) on the safety and efficacy of methadone as first-line treatment of cancer pain in a palliative care unit in Argentina found methadone to be a preferable first-line cancer-related pain treatment due to its effectiveness at low cost. Compared with other opioids, methadone was associated with less opioid rotation (15% versus 50%) and a longer time to opioid rotation (20.6 days versus 9.0 days). The prospective, open-label study by Porta-Sales et al (14) assessed efficacy and safety of methadone as second-line opioid therapy in adults with cancer at a palliative care outpatient clinic. 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 morphine and are less predictable. There are large variations among individuals in pharmacokinetics. Accumulation occurs with repeated dosing and so adverse effects are delayed over time (15-17). The terminal elimination half-life of methadone varies from 13-58 hours (up to 120 in some patients) compared with 3-4 hours for morphine (18). This long half life time makes dose adjustment more difficult than 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 to display drug interactions with common cancer treatments than morphine because it is metabolised by the cytochrome P-450 enzyme group.

	Methadone is associated with cardiac toxicities associated with its effects on cardiac conduction: QTc prolongation, torsades de pointes, ventricular fibrillation (19, 20). Although 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 for QT prolongation (20).
Additional evidence: (not in the application)	In 1986, methadone was compared with morphine in a randomized-parallel open-label study for 14 days (21). Analgesic effects were similar, as well as the pattern of adverse effects with relatively stable dose of methadone (4-24 mg/day) while a substantial increase in dose was reported in patients administered morphine. Similar conclusions were achieved in a subsequent study in the same year (22). Mercadante et al. (23) evaluated the analgesic and adverse effects and the doses of methadone in comparison to morphine in a prospective randomized study. The authors reported the same results obtained by Ventafridda et al (21). A randomized, double-blind controlled trial by Bruera et al. compared the effectiveness and safety of methadone and morphine as first-line opioids for cancer pain (24). 103 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 produce 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 showed comparable efficacy to morphine with more adverse effects and higher number of dropouts, 40.8% vs. 31.5%. These studies, followed by another randomized trial by Mercadante et al. in 2008 (25) demonstrated comparable but not superior analgesia of methadone, with similar adverse effect profile. These studies indicated that, over time, the opioid escalation index was lower for methadone than for morphine and this can explain the reduced tolerance of methadone in respect to morphine. A 2014 systematic review by Taberna et al. (26) focussed on the role of methadone in pain management in elderly patients. The review identified seven articles but none of them were specific to methadone use in elderly patients with cancer. There are insufficient data on the use of methadone as an analgesic in the elderly with cancer. Poulain et al. (10) compared two methadone titration methods (stop-and-go vs. progressive) in patients with cancer-related pain who were inadequately relieved by or intolerant to Level 3 opioids where 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% and the rate of success/failure was approximately 40% at Day 4 in both groups. Authors concluded that methadone represents an effective and sustainable second-line alternative opioid for the treatment of cancer-related pain and the two methods of titration are comparable in terms of efficacy and safety. Haumann et al. (11) compared methadone and fentanyl in a randomized trial of 52 strong opioid naive patients with head-and-neck cancer with pain > 4 on the Numerical Rating Scale (NRS) and a neuropathic pain component. 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 the use of methadone at 1, 3 and 5 weeks compared to fentanyl. This difference was significant at 1 and at 3 weeks 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 conducted in 2006. It did not include any studies conducted in children. Due to heterogeneity in methods and comparisons, pooled quantitative synthesis of results was not possible.

	For the main comparison of methadone versus morphine, one study of 103 participants reported greater 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' (ie. pain score of 3 or less after treatment) based on mean pain scores. Two studies of 148 participants reported mean scores close to 3. Quality of the evidence was considered to be low, downgraded due to 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 (appetite, thirst, somnolence) was not estimable and the quality of evidence rated very low (downgraded due to risk of bias and imprecision (as for efficacy) and also for indirectness with surrogate measures for the outcomes of interest being used). 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 maybe 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. 2012 WHO 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 with medical illnesses (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 the route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, low quality evidence). Alternative opioids to morphine included in the guidelines include fentanyl, hydromorphone, methadone and oxycodone. Administration by the oral route is recommended.
Costs / cost-effectiveness:	No information regarding costs or cost-effectiveness were provided in the application. MSF Drug Price Indicator 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$0.1247. De Lima et al (29) studied the global availability and prices of opioids in a cross-sectional study. Oral methadone was found to be the least expensive of the five opioids studied (morphine, methadone, fentanyl, hydromorphone and oxycodone) with a median price for 30-days of treatment of US$ 0.5. In comparison, the median price for 30-days treatment of immediate release oral morphine tablet/capsule 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 a new cancer pain guideline that is 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 represent a suitable alternative as an inexpensive and widely available treatment option to morphine. The Committee noted that the use of methadone could require training in the use of this medicine in countries. The Committee 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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UNEDITED VERSION

Tramadol (addition) – 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:	Dr Carla Ripamonti, Fondazione IRCCS, Instituto Nazionale Tumori, Milan, Italy and Dr Raffaele Giusti, Medical Oncology Unit, SantÁndrea Hospital of Rome, Italy
WHO Technical Department:	WHO Department of Mental Health and Substance Abuse
EML / EMLc	EML and EMLc
Section:	2.2 Opioid analgesics
Dose form(s) & strengths(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, eg. 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 alternatives to morphine under a square box listing. Tramadol is a synthetic opioid agonist with affinity to mu-opioid receptors. It also has non-opioid properties through inhibition of serotonin and noradrenaline reuptake that are thought to contribute to its analgesic effect (1). It is less potent than morphine, with the relative potency of morphine to tramadol being 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 cancer symptom which occurs 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, with 70% of deaths from cancer occurring in low- and middle-income countries (LMICs). 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 for use in cancer pain in order to help increase access to opioid pain relief for cancer patients. The applicant noted that the available evidence on the use of tramadol in cancer pain is poor, but also noted that oral tramadol is often available in countries where morphine is not (due to 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 low- and middle-income countries (LMICs) (8, 9).

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Summary of evidence: benefits (from the application)	The application presented the findings of a literature search of papers published in the last five years of tramadol and cancer pain. Bandieri et al (10) randomized 240 opioid-naive patients with cancer to receive either a weak opioid (tramadol, tramadol in combination with paracetamol, or fixed-dose combination of paracetamol and codeine) or low-dose oral morphine for 28 days. The primary endpoint was the number of 'responders' at 28 days or end of observation, whichever came first. Responders were defined as patients who experienced a 20% or greater reduction of 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% Cl, 3.12 to 12.24; $p < 0.001$). A systematic review by Koyyalagunta et al (11) 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, based on three low-quality studies. A prospective open label study by Husic et al (12) evaluated the efficacy of a fixed dose combination of tramadol and paracetamol in 353 advanced cancer patients. 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 treatment. The evidence presented in the application for tramadol was highly heterogeneous, with different comparisons, outcome measures and effect scales used making it difficult to accurately determine the magnitude of benefit.
Summary of evidence: harms (from the application)	Common adverse effects associated with opioid therapy are also seen with tramadol including sedation, constipation and respiratory depression. Severe respiratory associated with tramadol has been reported in children (13) and in a case report of one adult with cancer pain and renal insufficiency (14). Hyponatremia has also been observed during tramadol treatment (15-17). Tramadol, at normal doses, has been associated with seizures (18). Serotonin toxicity may occur when tramadol is given concomitantly or within 14 days of mono-amine oxidase inhibitors (MAOIs), and other medicines that increase serotonin activity (19). Tramadol abuse and trafficking has become a serious problem in many countries, where it is widely available and not subject to stricter controls, particularly in Africa and the Middle East and 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 the RCT by Bandieri et al. comparing morphine to weak opioids for moderate cancer pain, both treatments were found to be well tolerated. There were no differences observed in the intensity and frequency of opioid-related effects between treatment groups. The authors concluded both treatments to be well tolerated, with few discontinuations due to adverse events (10). In a RCT by Rodriguez et al, tramadol 200 mg per day was compared with hydrocodone + acetaminophen 25 mg + 2500 mg per 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 to 2.77), vomiting (RR, 2.21; 95%CI 1.14 to 4.32), and dizziness (RR, 2.12; IC 95%, 1.17-3.86) was significantly greater in the tramadol arm. Similar results were found in a second 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 has been raised in recent studies in both experienced drug users, and in patients with no history of substance abuse (23, 24).
WHO Guidelines:	The WHO Guidelines for Management of Cancer Pain are currently under review. 2012 WHO 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 with medical illnesses (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 the route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, low quality evidence). Alternative opioids to morphine included in the guidelines include fentanyl, hydromorphone, methadone and oxycodone. Administration by the oral route is recommended.
Costs / cost-effectiveness:	No information regarding costs or cost-effectiveness is provided in the application. MSF Drug Price Indicator 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.
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 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 the facilities sampled. 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 a new cancer pain guideline that is due for completion 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 subjected. The Expert Committee considered that the evidence presented in the application shows tramadol is a sub-optimal treatment for cancer pain compared to 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 – addition – 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:	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) & strengths(s):	Oral dose forms, tablets and capsules: 100mg, 200mg, 300mg, 400mg, 600mg, 800mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 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 Global Burden of Disease 2013 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 in the order of 7% to 10% (5). However, prevalence data based on self-reported information lack the ability to sort out the joint influence of incidence and survival, whereas studies conducted among clinical or referral series may include patients not representative of the population with the disease (e.g. diabetes). The provided estimates appear to substantially overestimate the burden of disease. Few studies evaluated the incidence through appropriate methods, particularly adopting a standard process to confirm the diagnosis cases in general populations. In two European studies (6, 7), the incidence per 10,000 person-years were 3.0 (95% confidence interval (CI) 3.0 to 3.1) and 4.2 (95%CI 3.8 to 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. The estimates vary largely from the estimates provided in the application. The former estimates 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).

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Summary of evidence: benefits (from the application)	The application included data on the following medicines: tricyclic antidepressants (TCAs amitriptyline), serotonin–noradrenaline re-uptake inhibitors (SNRIs; mainly duloxetine), pregabalin and gabapentin. All these medicines were considered as first-line options for neuropathic pain. Among these, the only medicine currently included in the EML is amitriptyline. The evidence supporting the application was based upon 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 unpublished trials. A supplementary search of PubMed was conducted on February 26, 2016 to update the application results. The population included in the trials was patients of any age with neuropathic pain according to the International Association for the Study of Pain 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) with at least 3 weeks of treatment. 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 neuroaxial 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). One hundred and twenty-seven (55%) of 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 to 5). Studies were associated with potential or established major shortcomings in several dimensions: 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. The application used the 'trim and fill' method to correct for funnel plot asymmetry arising from publication bias. The trim-and fill method suggested 34 theoretical missing studies. The overall effect size of benefit was reduced from an odds ratio of 1·8 (95% CI 1·7–1·9) to 1·6 (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, are based on the assumption 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), 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 to 5.3), gabapentin: 6.3 (95% CI: 5.0 to 8.3), pregabalin: 8.8 (95% CI: 7.5 to 10.8), SNRIs: 6.4 (95% CI: 5.2 to 8.4)]. In total, the assessment of gabapentin was based on 14 randomized controlled trials of gabapentin (900 to 3600 mg/day). The trials were predominantly conducted 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 to 8.3), and there was no evidence of a dose-response effect. The application provided data also on head-to-head trials of gabapentin and tricyclic antidepressants, 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 another systematic review. The Cochrane review by Moore et al (15) partitioned the analysis according to pain aetiology, 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 to 12) and painful diabetic neuropathy (NNT 5.9, 95% CI: 4.6 to 8.3). The authors concluded that there were insufficient data in other pain conditions, including fibromyalgia, to reach any reliable conclusion.
Summary of evidence: harms **(from the application)**	The analysis of adverse effects in trials of gabapentin for neuropathic pain was based on the meta-analysis by Finnerup et al (10). The combined number needed to harm (NNH) was based on 11 studies and was 25.6 (95% CI: 15.3 to 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 examining specific adverse events, dizziness, somnolence (or drowsiness or sedation), and in a few studies, peripheral oedema and confusion, had a prevalence > 10% and a higher prevalence than in the placebo group. The NNH for dizziness was 5.1 (95% CI: 4.3 to 6.3) and for somnolence 7.1 (95% CI: 5.7 to 9.4). In the Cochrane review of gabapentin in fibromyalgia and neuropathic pain by Moore et al, 62% of gabapentin-treated persons and 50% of persons given placebo experienced at least one adverse event in 17 studies with 4,002 participants. The risk ratio (RR) for adverse events was 1.25 (95% CI: 1.2 to 1.3), and the NNH was 8.6 (95% CI: 6.8 to 12). Serious adverse events were not more common for gabapentin than for placebo RR = 1.2, 95% CI: 0.8 to 1.7). The NNH for somnolence, drowsiness, or sedation was 11 (95% CI: 9.4 to 14; 4125 participants), for dizziness 7.6 (95% CI: 6.6 to 8.8; 4125 participants), and for peripheral oedema 21 (95% CI: 16 to 30; 3220 participants). Gabapentin was associated with an increased risk of ataxia or gait disturbance with and NNH of 13 (95% CI: 9 to 24; 544 participants) (15).
Additional evidence: **(not in the application)**	In 1993, gabapentin (Neurontin®, Pfizer, Inc.) was first approved by the FDA as an adjunctive therapy for epilepsy. In 2002, the drug was approved for the management of postherpetic neuralgia, its only indication related to pain. 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). The promotion was judged to be illegal and fraudulent: in 2004, American pharmaceutical manufacturer Warner-Lambert agreed to plead guilty and pay more than $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 litigations, internal company documents related 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) which documented publication and outcome reporting biases, and data manipulation. The magnitude of these biases is highly relevant, and impacts on the evidence presented in the application. Firstly, in 2009 out 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 related 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 ten trials the numbers of participants randomized and analyzed for the primary outcome and the type of analysis for efficacy and safety in both the internal research report and the trial publication differed. Different subsets of participants were included in the analysis, thereby 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 imbalanced the comparisons, favouring responsive patients and excluding poor responders in the arms allocated to gabapentin, thereby inflating the effect size 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:	There are not currently any WHO guidelines for the treatment of neuropathic pain. Guidelines from the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP) (10), the National Institute for Health and Care Excellence (NICE), UK (24) and European Federation of Neurological Societies (25) report that tricyclic antidepressants, α2δ calcium channel ligands (gabapentin and pregabalin), and selective serotonin and noradrenaline re-uptake inhibitors should be considered first-line therapy, with the choice of medicine being guided by clinical and therapeutic factors (e.g., contraindications, interactions), and medicine availability and affordability.
Costs / cost-effectiveness:	Comparative pricing data were obtained from the Management Sciences for Health (MSH) International Drug Price Indicator Guide (26). Prices based on the defined daily dose (DDD) of gabapentin varied from US $ 0.36 to 2.31. Prices of amitriptyline varied from US $ 0.04 to 0.34. Analysis of comparative pricing for gabapentin was limited by the absence of price data from suppliers, and price data was only available from one buyer source each for the 100mg and 400mg doses of gabapentin, and three sources for the 300mg dose. Cost-utility analysis: The National Institute of Health and Care Excellence, UK (NICE), recently completed a cost-utility analysis across treatments typically recommended as first-line for neuropathic pain (24). Medicine prices were taken from the National Health Service, UK Electronic Drug Tariff register for March 2013, and health benefit was valued in quality-adjusted life-years (QALY). 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: US Federal Drug Administration (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 the PMDA and Health Canada only indicate gabapentin for the treatment of epilepsy. Regulatory approval of gabapentin for neuropathic pain Registration authority: Indication for pain FDA, US: Postherpetic neuralgia EMA, European Union: Neuropathic pain TGA, Australia: Neuropathic pain PMDA, Japan: No Health Canada: No
Other considerations:	The Committee acknowledged the serious issues on publication and outcome reporting bias as important ones.
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

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	on the basis 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 child-bearing aged women 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 new onset partial or generalized epilepsy.
Applicant:	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 WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development, Bologna Italy
WHO Technical Department:	Department of Mental Health and Substance Abuse
EML / EMLc	EML and EMLc
Section:	5. anticonvulsants/antiepileptics
Dose form(s) & strengths(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
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	The WHO EML currently lists nine anticonvulsant medicines: carbamazepine, diazepam, lorazepam, magnesium sulfate, midazolam, phenobarbital, phenytoin, valproic acid and ethosuximide (the latter is only in the complementary list). The same drugs, except for magnesium sulfate, are in the WHO EMLc. These drugs are intended to treat generalized and partial epilepsy, mostly as first-line therapies. Past WHO EML Expert Committees 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). Among the anticonvulsants not included in the EML and EMLc, none can be considered as the treatment of choice in generalized as well as partial seizures, and "treatment strategy should be individualised 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). The inclusion in the EML and EMLc of suitable treatments that may be added as second-line therapies in drug-resistant epilepsies, and also used as alternative first-line options if treatments now included in the EML-EMLc are not available or not tolerated, is desirable. The application was preceded by an overview of recently updated guidance on epilepsy, finding 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 forms. Therefore, lamotrigine was selected as priority candidate to the EML, considering 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 an antiepileptic drug (AED)

	of the phenyltriazine class chemically unrelated to existing AEDs.
Public health relevance: (burden of disease)	Epilepsy is a chronic disorder of the brain affecting both sexes and all ages, characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, 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 the 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 1,000 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, whereas in developing countries incidence peaks among children and young adults. This is probably due to a higher exposure to some preventable risk factors (i.e. perinatal risk factors, infections, traumas), and also reflects 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 precise diagnosis remains difficult. Epilepsy can be associated with significant morbidity due to the effects of seizures and/or treatment. Epilepsy is associated with stigma and relevant psychological, social, cognitive, and economic repercussions. People with epilepsy commonly encounter problems in the following areas: education; employment; driving; personal development; psychiatric and psychological aspects and social and personal relationships (2). Moreover, it has to be noted that epilepsy may be the manifestation of an underlying pathology (e.g. stroke, tumour, cerebral palsy, infection, etc.). Deaths related to epilepsy may be attributable to underlying disorders (causing a symptomatic epilepsy), or to the epilepsy itself, as in chronic epilepsy. In developed countries, mortality among epileptic patients measured as a standardized mortality ratio (SMR) is 2–3 times higher than in the general population and, up to six-fold higher in developing countries (7, 8). The diagnosis of epilepsy is primarily clinical and based on a detailed description of the events before, during and after a seizure given by the person and/or witness. Seizures are generally described in two major groups: primary generalized seizures (including tonic-clonic seizures) and partial seizures. Therefore, the availability of an AED showing effectiveness in both types of seizures and in pediatric as well as adult patients would be a useful treatment option in clinical practice, since it could be offered to the majority of persons with epilepsy.
Summary of evidence: benefits (from the application)	The mainstay of treatment for epilepsy is AEDs to prevent the recurrence of epileptic seizures without adverse effects (9). Given the wide variability in the frequency and severity of seizures of epilepsy syndromes, defining treatment success is not an easy task. Treatment success has been defined by ILAE as a seizure free duration that is at least three times the longest seizure free interval prior to starting the new 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, therefore a frequency of one seizure per year can 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, and if the first AED is not

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effective or not tolerated, a trial of a second AED is recommended. It is preferable to maintain a patient 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 a challenging task due to the fact that most clinical trials on AEDs compare the active treatment with placebo and therefore direct comparisons among them are not always available. The relative efficacy of new compounds has to be inferred by means of systematic reviews and meta-analyses, but such comparative effectiveness research shows a lack of conclusive evidence to determine a prescribing hierarchy accounting for differences in efficacy or tolerability.

The application searched for systematic reviews (SRs), randomized controlled trials (RCTs) not included in SRs, 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 distribution of the aetiology of epilepsy and of the characteristics of patients at risk is different from that of developing countries.

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

Available evidence comes from RCTs testing the addition of lamotrigine versus addition of placebo to current therapy. Specifically in drug resistant generalized epilepsy addition of lamotrigine to current anticonvulsivant therapy was found to be “likely to be beneficial” (GRADE quality of evidence: moderate), for being superior to addition of placebo in reduction of seizure frequency in three placebo-controlled RCTs (11). Studies included both adults and children but did not report outcomes separately. The three studies were not meta-analyzed due to differences in study design. All three RCTs found that, in people with generalised tonic-clonic or absence seizures, adding lamotrigine significantly increased the proportion of people with a 50% or greater reduction in seizure rate. 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: first RCT, over dose-escalation and maintenance phase, 64% with lamotrigine versus 39% with placebo; $P < 0.05$; intention-to-treat analysis (12); second RCT, 75% with lamotrigine versus 32% with 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 addition of lamotrigine to current anticonvulsant therapy was found to be superior to addition of placebo in reduction of seizure frequency (GRADE quality of evidence: high) in a Cochrane systematic review, including 14 RCTs which involved both adults and children (38 infants, 199 children, and 1721 adults, for a total of 14 studies included 1958 participants) (15). The overall risk ratio (RR) for participants with 50% or greater reduction in seizure frequency was 1.80 (95% CI 1.45 to 2.23) for twelve studies (n = 1322 participants, 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 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 does not delay time to first seizure as much as carbamazepine (GRADE quality of evidence: low). Results for generalized epilepsy suggest that valproate might be the best choice: time to 12-month remission occurred significantly less rapidly on lamotrigine monotherapy compared to sodium valproate (moderate quality

	evidence). These results overlap with the SANAD trial (17). A Cochrane systematic review published in 2016 compared lamotrigine and carbamazepine. It included individuals with partial onset seizures, and showed mixed results: a significant advantage for carbamazepine compared to lamotrigine for time to first seizure (hazard ratio (HR) 1.22, 95% CI 1.09 to 1.37) and for time to six-month remission (HR 0.84, 95% CI 0.74 to 0.94) but a significant advantage for lamotrigine for withdrawal of allocated treatment (HR 0.72, 95% CI 0.63 to 0.82) (18). A network meta-analysis published in 2016, making multiple comparisons between AED, found that lamotrigine was not different from other new AEDs (e.g. levetiracetam, oxcarbazepine, sulthiame, and topiramate) or carbamazepine in terms of efficacy profiles (19). One subsequent RCT which 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 followup, 23 (76.67%) patients taking valproic acid and 17 (56.67%) patients taking lamotrigine were seizure-free. Statistical analyses were doubtful: re-analyses of data provided non-significant differences between groups (RR 1.22, 95% CI 0.86 to 1.73) (20). Another subsequent large RCT, which compared the effectiveness of lamotrigine versus controlled-released carbamazepine and levetiracetam in 359 patients older than 60 years with newly diagnosed focal epilepsy found that retention of lamotrigine was not significantly different between either comparators, and seizure freedom rates at weeks 58 were not 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 increases side effects. The adverse events significantly associated with lamotrigine were: ataxia, dizziness, diplopia, and nausea. The RR of these adverse effects were as follows: ataxia 3.34 (99% CI 2.01 to 5.55; 12 RCTs; n = 1524); dizziness 2.00 (99% CI 1.51 to 2.64; 13 RCTs; n = 1767); diplopia 3.79 (99% CI 2.15 to 6.68; 3 RCTs; n = 943); nausea 1.81 (99% CI 1.22 to 2.68; 12 RCTs; n = 1486) (15). Another review, in addition to the adverse events already mentioned, rash and headaches were the other common side effects reported. Skin reactions were confirmed by open-label studies, also in children (22, 23). **Lamotrigine versus other anticonvulsivants as monotherapy** In monotherapy, a NICE systematic review (updated 2014) (2) showed that, compared to other anticonvulsants, lamotrigine was better tolerated than carbamazepine, phenobarbital, gabapentin (except for skin rash) and topiramate (GRADE quality of evidence from very low to moderate). A Cochrane systematic review published in 2016 specifically comparing lamotrigine and carbamazepine, mostly including individuals with partial onset seizures, showed a significant advantage for lamotrigine compared to carbamazepine for time to withdrawal (9 RCTs; HR 0.72, 95% CI 0.63 to 0.82; GRADE quality of evidence: moderate) (18). The latter result was confirmed by a network meta-analysis of RCTs published in 2016, showing 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: Anti-epileptic 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 case of monotherapy treatment of epilepsy in pregnancy. This review included prospective cohort controlled studies, cohort studies set within pregnancy registries and randomised controlled trials (25). Children exposed to lamotrigine in utero were not found to be at increased risk for major malformation compared with children born to women without epilepsy and to women with untreated epilepsy. As for drug-drug comparisons, children exposed to

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	lamotrigine were at lower risk than children exposed to valproic acid (VPA) (N = 4164 vs 2021, RR VPA vs LTG 3.56, 95% CI 2.77 to 4.58), carbamazepine (CBZ) (N = 4164 vs 3385, RR CBZ vs LTG 1.34, 95% CI 1.01 to 1.76), phenobarbital(PB) (N = 1959 vs 282, RR PB vs LTG 3.13, 95% CI 1.64 to 5.88), phenytoin (PHE) (N = 4082 vs 624, RR PHE vs LTG 1.89, 95% CI 1.19 to 2.94) and topiramate (TPM) (N = 3975 vs 473, RR TPM vs LTG 1.79, 95% CI 1.06 to 2.94). These data are reassuring and also show that lamotrigine is safer than most other AEDs. Additionally, a higher number of observations is available for lamotrigine than for other AEDs: gabapentin, levetiracetam, oxcarbazepine, primidone or zonisamide were not associated with an increased risk, but there were substantially fewer data for these medications. On the other side, children exposed to carbamazepine, phenytoin, and valproic acid were at a higher risk of malformation compared with children born to women without epilepsy and to women with untreated epilepsy. Similarly, children exposed to phenobarbital and topiramate were at a higher risk of malformation compared with children born to women without epilepsy. For example, children exposed to valproic were at a higher risk of malformation compared with children born to women without epilepsy (N = 467 vs 1936, RR 5.69, 95% CI 3.33 to 9.73) and to women with untreated epilepsy (N = 1923 vs 1259, RR 3.13, 95% CI 2.16 to 4.54). A concurrent population-based case–malformed control study, based on 21 EUROCAT congenital anomalies (CA) registries covering 10.1 million births in Europe (1995–2011) and a total of 226,806 babies with CA, suggested that orofacial cleft (which had been previously hypothesized following a pooled analysis from five pregnancy registries including 1623 pregnancies) and other CA were not significantly associated with lamotrigine monotherapy, except for a possible association with clubfoot (adjusted odds ratio (ORadj) 1.83; 95% CI 1.01–3.31) (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 AE, occurring in 7.3% of the patients. Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients. Discontinuation due to an adverse drug reaction was recorded in 72 children (1.9% of all treated patients). These data are quite reassuring, although the possibility of occurrence of Stevens-Johnson syndrome (in about one of 1000 cases) should be carefully considered. Persons with HIV/AIDS and epilepsy In persons infected with HIV the occurrence of seizure disorders is increased, with an incidence of about 6% (28). Clinically significant drug interactions can occur when antiretroviral agents are combined with enzyme-inducing AEDs, such as carbamazepine, phenytoin, and phenobarbital. These interactions can result in altered serum levels of both AEDs and antiretroviral agents, and can lead to higher rates of HIV treatment failure compared to use of antiretroviral agents with non-enzyme-inducing AEDs. In persons with HIV/AIDS treated with antiretroviral drugs the use of 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 occurring in adults and paediatric patients taking lamotrigine were reported from 1994 to 2009, out of over 46 million prescriptions dispensed (31).
Additional evidence: **(not in the application)**	N/A
WHO Guidelines:	Lamotrigine is included in the 2015 update of the WHO Mental Health Gap Action Program (mhGAP) Guideline 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).

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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 the Health Action International), the cost per 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 as cost-effective treatments for the UK NHS: • lamotrigine and oxcarbazepine for adjunctive treatment in children, young people and adults with refractory focal seizures; • lamotrigine for newly diagnosed focal seizures who require treatment • lamotrigine has the lowest total cost and is likely to be cost-effective for first-line treatment in children, young people and adults with newly diagnosed generalised tonic clonic seizures Considering that no other relevant comparative economic evidence was found, and although they refer to the UK NHS, these analyses suggest that lamotrigine may be a cost-effective anticonvulsant drug in different clinical scenarios comparing to the available alternatives.
Availability:	Lamotrigine was approved by the Food and Drug Administration in the USA in 1994 for use in partial-onset seizures. It was ultimately approved for monotherapy in 1998. EMA, but not FDA , licensed lamotrigine as monotherapy in generalized seizures.
Other considerations:	Topiramate and lamotrigine are the two drugs with the broadest indications, both in pediatric and adult populations.

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

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 demonstrated to be an effective medication 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. It also noted that lamotrigine has been reported to be a valid alternative as monotherapy to carbamazepine and valproate. Its safety profile for use in women of child-bearing age and people living with HIV/AIDS appears favourable compared to other therapeutic options included in the EML/EMLc. Considering all relevant clinical outcomes, there is a net benefit resulting primarily from lamotrigine's safety profile. Based on the positive evaluation, the Expert Committee therefore recommended 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 comparative effectiveness and safety review of lamotrigine 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 – new indication – EML and EMLc

Ivermectin	**ATC Code: P02CF01**
Proposal:	The application proposed inclusion of ivermectin on the EML and EMLc for a new indication as an intestinal anthelminthic for use against *Strongyloides stercoralis*, and in combination with albendazole for use against soil-transmitted helminthiasis (STH). The goal for the addition of ivermectin to the EML and EMLc for strongyloidiasis is predominantly for 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 using large scale 'mass drug administration (MDA)' programmes.
Applicant:	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) & strengths(s):	Tablet (scored): 3 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 combat hepatitis, water-borne diseases and other communicable diseases. <u>Strongyloidiasis</u> Is globally distributed and is endemic in the tropics and subtropics (1, 2). An estimated 30–100 million people are infected worldwide; precise data on prevalence are unknown 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, impaired growth, and cognitive development of children and poor school performance. Heavy worm infection is associated with anaemia in children. <u>Soil-transmitted helminthiasis</u> The global target is to eliminate morbidity due to STH in children by 2020. This will be obtained by treating at least 75% of the children in endemic areas (an estimated 873 million) (3). The STH disease cluster is considered the most widespread neglected tropical disease 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 over 100 endemic countries (4, 5). There are 3.3 million disability-adjusted life years (DALYs) attributed to STH infection due to symptomatic infection, wasting, mild abdominopelvic problems and anaemia (4, 6).

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	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 includes four studies comparing ivermectin versus 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% CI 1.55 to 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 versus thiabendazole. The results showed little difference in parasitological cure (RR 1.07, 95% CI 0.96 to 1.20; 467 participants, low quality evidence). The review found that single dose ivermectin (200 micrograms/kg) was associated with the same rate of parasitological cure as two-dose ivermectin treatment (RR 1.02, 95% CI 0.94 to 1.11). However, the review noted that this result was based on only two trials with a small number of participants (n=94). Soil-transmitted helminthiasis (STH) 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 (EERs, when available) were extracted of 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. In these two studies the co-administration of albendazole-ivermectin revealed a CR of 79.8% against *A. lumbricoides* infections versus a CR of 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) including 342 patients revealed a CR of 47% against *T. trichiura* infection with co-administration of albendazole-ivermectin compared to albendazole alone (RR 0.53, 95% CI 0.37 to 0.76). EERs in these three studies ranged from 91.3% to 99.7% for albendazole-ivermectin, compared with 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 co-administration is more effective at curing hookworms than albendazole alone. However, in terms of ERRs, the difference is small: 95.9% with the co-administration and 94% albendazole alone. Other studies compared the efficacy of ivermectin alone against *T. trichiura* (CR: 52.7% and ERR across the four studies ranged from 58.9% to 98.2%) (11, 15-17); *A. lumbricoides* (CR: 90.3% and ERR 100%) (11, 15, 16); and hookworms (CR: 24.6%, and ERR: 80% reported in one study) (15-17). The application concluded that the evidence demonstrates ivermectin to be a highly efficacious treatment of strongyloidiasis, with greater efficacy than albendazole, mebendazole and thiabendazole and increased efficacy in children under 5 years of age. For STHs, the application stated that ivermectin administered with albendazole is more efficacious at treating *T. trichiura* than albendazole alone, and mostly comparable to albendazole alone for treatment of *A. lumbricoides* and hookworm.

Summary of evidence: harms (from the application)	Strongyloidiasis In the four studies comparing ivermectin with albendazole in the Cochrane systematic review (8), there were no statistically significant differences in adverse events (RR 0.80, 95% CI 0.59 to 1.09; 518 participants, low quality evidence). In the three trials comparing ivermectin with thiabendazole, adverse events were less common with ivermectin (RR 0.31, 95% CI 0.20 to 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 110 μg/kg 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/kg group, liver dysfunction was observed in 6.5% (6/92) of patients. The abnormalities were mild, transient and not clinically important in both groups. Soil-transmitted helminthiasis (STH) Four studies compared the safety of the co-administration of albendazole-ivermectin to that of albendazole alone (13, 19-21). Although not significant, co-administration was associated with more AEs than albendazole alone. Similarly, but also not significant, the co-administration was associated with more AEs than ivermectin alone (19, 20). The frequency and severity of AEs have been shown to be associated with baseline infection status, intensity of infection, and infection-related immunie response parameters. For example, when administered to subjects with high *Loa loa* microfilariaemia, 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. There were a total of 1656 reports for ivermectin in VigiBase, of these 525 (31.7%) contained both ivermectin and albendazole, which mostly originated from Sierra Leone (397). Between 2007 and 2015, there have been over 33 million tablets of ivermectin administered with albendazole in the lymphatic filariasis programme. This corresponds to approximately 11 adverse events per one million treatments, without taking into account drugs administered before 2007 or in 2016. All of these reported events were considered minor. The most commonly reported ADRs for ivermectin alone and ivermectin co-administered with albendazole included pruritus, headache, dizziness, vomiting, rash, urticarial and diarrhoea. In total, 459 reports of ivermectin were reported to have a serious ADR. Sixty three resulted in death (likely due to causes other than ivermectin itself). Concomitant medication was frequently administered. The most frequent ADRs reported in cases that resulted in death included strongyloidiasis, drug ineffective, 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 sick individuals is recommended (7). It is recommended that ivermectin not be administered to children less than 90 cm tall or weighing less than 15kg, pregnant women, lactating women in the first week after birth and 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 for STH treatment (albendazole or mebendazole) (7).
Costs / cost-effectiveness:	According to the MSH International Drug Price Indicator Guide, in 2013, the median buyer price per tablet for ivermectin 3 mg was US$ 0.0296.

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	For large-scale treatment of STH infection, the application asserted that adding ivermectin to albendazole that is already being delivered for MDA programmes will involve only marginally increased costs, namely those associated with ivermectin purchase, and will 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 to harm ratio, and the public health impact of ivermectin in the treatment of intestinal helminth infections. The Expert Committee recommended adding ivermectin on the EML and EMLc under the section intestinal anthelminthic for use against *Strongyloides stercoralis* and STH. It may be used in combination with albendazole for treatment of soil-transmitted helminthiasis.

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6.2 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:

1) a review of antibiotics for 21 priority infectious syndromes in adults and paediatrics conducted by the Department of Health Research Methods, Evidence and Impact, McMaster University, Canada (the 'McMaster Group');

Infectious syndromes reviewed: McMaster Group		
Community acquired pneumonia	Urinary tract infection (UTI)	Surgical site infections
Pharyngitis	Catherer-associated UTI	Cellulitis
Sinusitis	Endocarditis	Acute infectious diarrhoea
Otitis media	Meningitis	Sexually transmitted diseases
Hospital acquired pbneumonia	Central-line inrfections	Exacerbations of COPD
Ventilator associated pneumonia	Complicated intra-abdominal infections	Bone and joint infections
Sepsis in children	Wound, skin and soft tissue infections	Febrile neutropenia

2) a review of antibiotics for five specific bacterial infections in paediatrics based on a review of WHO guidelines conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health;

Infectious syndromes reviewed: WHO Department of Maternal, Newborn, Child and Adolescent Health		
Community acquired pneumonia	Dysentery	Severe acute malnutrition (SAM)
Sepsis	Cholera	

3) a review of antibiotics for specific sexually transmitted infections based on a review of updated WHO guidelines, conducted by the WHO Department of Reproductive Health and Research:

Infectious syndromes reviewed: 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 however noted that the methodology - based on published systematic reviews and higher quality guidelines - provided limited information on antibiotic selection in the LMIC setting.

The Expert Committee included clinical infection syndromes requiring antibiotics that are commonly encountered globally. The main focus was on empiric treatment choices for common, important (mostly) community-acquired infections that are broadly applicable in the majority of countries. Antibiotic prophylaxis, in particular surgical prophylaxis, was not considered as a part of this review as this is the subject of a WHO guideline in development by the department of Service Delivery and Safety.

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The recommendations for the Model Lists are not guidelines, and the recommended empiric 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, alternative options for 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 Committee noted that the prescription of any antibiotics has to balance the benefits and risks to the patients with the impact on public health.
- The terms 'core' and 'targeted', used in the application from the McMaster Group, were changed, for the following reasons:
    - 'core' for the EML/EMLc already has a definite meaning (i.e., core and complementary lists); and
    - 'targeted' in the infectious diseases world, means 'based on microbiology results'.
- Empiric therapy for each clinical infection syndrome includes **first and second choice** of antibiotics. The first choice antibiotics are those generally recommended based on available evidence and are usually narrow spectrum agents with positive benefit-to-risk ratios and low resistance potential. Second choices are more broad spectrum antibiotics with a less favourable benefit-to-risk ratio and higher resistance potential.
- First and second choice antibiotics were aligned to recent WHO guidelines on sexually transmitted infections (STIs; gonorrhoeae, 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 Committee designated antibiotics that are first or second choice antibiotics in at least one syndrome as key **"ACCESS"** antibiotics (Group 1, Table x), emphasizing their role as the antibiotics that should be widely available, affordable and quality assured.

Table x: Group 1 - ACCESS group antibiotics

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*			

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Italics = complementary list;
*Watch group antibiotics included in the EML/EMLc only for specific, limited indications

- The Expert Committee also wished to encourage the general principles of antibiotic stewardship in all sectors. In this regard, the Committee wished to build on and reflect the important work taken forward in designation of the WHO List of Critically Important Antimicrobials for Human Medicine (WHO CIA List) (1), aiming at preserving medically important antimicrobials used in food animal production, for clarity and cross-referencing purposes. The intent and purpose of the EML and EMLc includes different factors than those considered by the WHO CIA List. While the EML and EMLc take into account bacterial resistance, they also include issues of efficacy and access. The purpose of the WHO CIA List was to assess the impact of resistance as well as the risk of transmission through the food chain. Hence while there is considerable overlap between the two lists, there will be inevitable differences as well, including the names of antibiotic groupings.
- To assist 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"** and a more focussed **"RESERVE"** stewardship groups could assist in activities such as local, national and global monitoring of use, development of guidelines and educational activities.
- The Stewardship **"WATCH"** group (Group 2, Table y) 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 programs and monitoring. This group includes the highest priority agents on the list of Critically Important Antimicrobials (CIA) for Human Medicine (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.

Table y: Group 2 - WATCH group antibiotics
Quinolones and fluoroquinolones - e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin These antibiotics are considered highest priority critically important antimicrobials on the WHO CIA List and carry a high risk of selection of bacterial resistance (in particular MRSA, ESBL, and resistance to fluoroquinolones). **Ciprofloxacin** is listed on the EML(c) as a first-choice option for acute invasive bacterial diarrhoea/dysentery, low-risk febrile neutropenia, pyelonephritis or 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-lactamase inhibitor) - e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime These antibiotics are considered highest priority critically important antimicrobials on the WHO CIA List and carry a high risk of selection of bacterial resistance (in particular ESBL). **Ceftriaxone** is listed on the EML(c) as a first-choice option for 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), and

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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(c) for the same indications as ceftriaxone, except *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 WHO CIA List and carry a high risk of selection of bacterial resistance (in particular resistance to macrolides). Given its remarkably long half-life, azithromycin carries the higher risk of resistance among the macrolides. **Azithromycin** is listed on the EML(c) as a first-choice option for trachoma, yaws, *Chlamydia trachomatis*, cholera, *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*, 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 WHO CIA List and have high risk of selection of bacterial resistance (e.g., vancomycin-resistant enterococci (VRE)). **Vancomycin** is listed on the EML(c) as a second-choice option for *Clostridium difficile* infections and high-risk febrile neutropenia.
Anti-pseudomonal penicillins with beta-lactamase inhibitor - e.g. piperacillin + tazobactam These antibiotics have a broad spectrum and activity and carry a high risk of selection of bacterial resistance. **Piperacillin + tazobactam** is listed on the EML(c) as a first-choice option for complicated intraabdominal infections (severe), high-risk febrile neutropenia and hospital acquired pneumonia.
Carbapenems - e.g. meropenem, imipenem + cilastatin **Penems** – e.g. faropenem Carbapenems have a wide 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 intraabdominal infections and high-risk febrile neutropenia. **Imepenem + cilastatin** is an alternative in some cases. No penems are included on the EML or EMLc.

- The more focused Stewardship **"RESERVE"** group (Group 3, Table z), was added to the list identifying antibiotics and antibiotic classes based on their "last resort" status (antibiotics or antibiotic classes to be used when other alternatives would be inadequate or have already failed (e.g., serious life-threatening infections due to multi-drug resistant bacteria)). This group was identified in order to improve targeted access according to available recommendations and reduce the risk of development of resistance to these last-resort antibiotics. These medicines could be protected and prioritized as key targets of high-intensity national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness. Eight antibiotics or antibiotic classes were identified for this group.

Table z Group 3 - RESERVE group ('last-resort') antibiotics	
Aztreonam	Fosfomycin (IV)
4th generation cephalosporins e.g. cefepime	Oxazolidinones e.g. linezolid

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5th generation cephalosporins e.g. ceftaroline	Tigecycline
Polymyxins e.g. polymyxin B, colistin	Daptomycin

Other considerations

- The Expert Committee noted there remain many barriers to reduction in broad spectrum antibiotic use. For example the Committee noted that allergy skin testing on all patients before penicillin use is required in some regions and recommended strongly against routine use of this practice. This practice is unnecessary, and it 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 Access antibiotics remains a major concern for both high- and low-/middle- income countries. Regular and prolonged shortages of antibiotics on the Access list are a threat to responsible antibiotic use, as they force clinicians to use broader spectrum antibiotics that are sometimes less efficacious and more toxic for patients.
- The Expert Committee noted that there remain major concerns about sub-standard and counterfeit medicines within the key Access 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 antibiotic use is a balance between best efficacy for the patient, and minimization of the risk of adverse effects, both for the patient (classical adverse events, C. difficile infections, bacterial resistance) and the population (bacterial resistance).
  - Antibiotic stewardship is a behaviour change strategy, and is thus a complex and system-wide intervention. Antibiotic stewardship programmes should use a combination of interventions, in all settings (primary care, hospitals), and at all levels (local, national, international). A single intervention is not enough, multiple interventions must be associated, and adapted to the local context. These programmes can have a positive impact, provided that sufficient resources are made available in a sustainable manner, with strong political and institutional support. However, disseminating recommendations at a local or national level is not enough, and a detailed and long-term implementation plan must be rolled out in order to bring change. Long-term monitoring of indicators is of course necessary to assess the impact of the stewardship programme, and to adapt it.
  - Antibiotic use is a complex interplay between patients, prescribers, and non-prescriber healthcare professionals, all influenced by their environment (i.e. system organisation, culture, regulation). An antibiotic stewardship programme must target the general public, healthcare professionals (whether they prescribe antibiotics or not), as well as policy-makers. It will try to change behaviour, which is notoriously a very difficult process, by acting both at the individual and system levels.
  - Several behavioural interventions can be used, for example:
    - system change intervention: having antimicrobial stewardship teams as a mandatory requirement in hospitals, or banning over-the-counter sale of antibiotics by law;

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- intervention targeting the general public: awareness campaigns;
- intervention targeting prescribers: education, audits and feedback, promotion of the use of guidelines (as only making guidelines available will not lead to a change in prescribing).

These are only examples, the range of interventions is of course much larger.

- 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 Stewardship Watch group, and applied more intensively for the Reserve group, to capture data on actual versus optimal use.
- The Expert Committee noted the need to further develop and expand on the key principles of access and stewardship with a standing EML(c) antibiotics working group.

The Expert Committee noted further work was required and 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;
- adapt or work on the current clinical synopsis reviews 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 for EML and EMLc;
- 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 programs.
- Scoping or making an inventory of key older antibiotics that may be considered important to add to the Reserve group.

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Community acquired pneumonia (CAP)

Community acquired pneumonia (CAP)	
Applicant(s):	McMaster Group WHO Department of Maternal, Newborn, Child and Adolescent Health
Introduction: Description of the condition / infecting organisms / public health need?	Community-acquired pneumonia (CAP) refers to pneumonia that is acquired in the community as compared to the healthcare system. Patients with advanced age, comorbid conditions, or with 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, there has been controversy over the need for so-called "atypical coverage" of pathogens such as *Chlamydia pneumoniae, Mycoplasma*, or *Legionella* with antibiotics such as macrolides or fluroroquinolones. The emergence of macrolide and fluroroquinolone resistance in the community has created concern and the need for these in addition to antibiotics with anti-pneumococcal 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)	<u>Adult outpatient therapy</u> A 2014 Cochrane review (11 RCTs of 3,352 participants older than 12 years with a diagnosis of CAP) reported that for outpatients, there was no benefit 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 compared to erythromycin (OR 0.3, 95%CI 0.2 to 0.46). The application did not propose erythromycin for inclusion on the EML for this indication for this reason. Substantially more adverse events with azithromycin (42/211) versus levofloxacin (26/211) (OR 1.78, 95%CI 1.04 to 3.03) were noted. Although adverse events, such as nausea and vomiting, are in themselves not life-threatening, they can have an important impact on adherence. There was no comparison of clarithromycin versus levofloxacin. Given these adverse effects, and the fact that the 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) mostly assessing outpatients with mild to moderate CAP found no difference in death between macrolides versus fluoroquinolones, RR 1.03 (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 therefore these findings do not help differentiate between these antibiotic classes. <u>Adult inpatient therapy</u> The approach to hospitalized patients differs from outpatients because of severity of illness and concern for complications. Coverage for atypical pathogens has been a source of controversy. A 2012 Cochrane review (28 RCTs of 5,939 participants) of empiric therapy for CAP in hospitalized adults showed that there was no additional benefit from atypical coverage versus typical coverage in reducing deaths (4). There was no difference between groups for mortality (RR 1.14; 95% CI 0.84 to 1.55), however only one study compared a beta-lactam to a beta-lactam and a macrolide. The width of the confidence intervals go beyond that specified by the applicants for similarity (i.e., within 5%) and therefore these results 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 to 0.92). A 2015 review (16 RCTs, 4,809 participants) reported no difference in mortality between fluoroquinolones and beta-lactam/macrolide combinations (RR 0.99, 95% CI 0.70 to 1.40) but wide confidence intervals limited inferences (5). However, they did report a reduction in clinical failure with fluoroquinolones RR 0.72 (95% CI 0.57 to 0.91). Overall, these findings may

be useful to clinicians in helping select antibiotics, but given that wide groups of antibiotics are being compared, were not considered helpful by the applicant 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 randomized controlled trial (6). This 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, during these strategy periods. The risk of death was higher by 1.9 percentage points (90% CI, −0.6 to 4.4) with the beta-lactam–macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, −2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated non-inferiority of the beta-lactam strategy. These data are of particular relevance, because it does not appear that atypical antibiotics added to beta-lactam antibiotics make a clinically important difference, at least for patients presenting with mild to moderately severe CAP.

Although 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 5 RCTs for inpatients addressed and reported no difference between flurorquinolones and macrolides for mortality (RR 1.13, 95% CI 0. 65 to 1.98) (7). Given that the confidence intervals are relatively wide, the results do not allow either protection or harm from flurorquinolones compared to macrolides.

<u>Children</u>

A 2013 Cochrane review of antibiotics within an outpatient or hospital setting (29 RCTs, 14, 188 children), showed that amoxicillin had similar cure rates compared to trimethoprim/sulfamethoxazole (TMP/SMX) (odds ratio (OR) 1.03, 95% CI 0.56 to 1.89) (8). 'Cure' in this review referred to an absence of symptoms at end of treatment, 'failure' was the presence of a sign at the end of therapy, while 'relapse' was defined as a cure in a patient who developed recurrence of disease in follow up. Given the wide confidence intervals, (i.e., beyond 10%), these data were not considered by the applicant to inform proposal of antibiotics for the EML. Amoxicillin resulted in better cure rates than amoxicillin+clavulanic acid (RR 10.44, 95%CI 0.29 to 38.2) suggesting that amoxicillin alone may be preferred.

Failure rate at 21 days was greater for chloramphenicol compared to ampicillin and gentamicin (OR 1.43, 95%CI 1.03 to 1.98). The applicants considered this important evidence to support non-inclusion of chloramphenicol on the EML and support inclusion of ampicillin and gentamicin. Cure rate was significantly greater for amoxicillin compared to cefpodoxime (OR 0.20, 0.08, 0.53). This favours inclusion of amoxicillin and argues against the inclusion of oral third generation cephalosporins on the EML.

Another systematic review examined very severe pneumonia for children in low- and middle income countries (LMIC), which showed no difference in death rates between ampicillin and gentamicin versus chloramphenicol (1 RCT, 2,074 children) (0.71, 95% CI 0.51 to 1.00) (9). However, the failure rate was reduced with ampicillin and gentamicin compared to chloramphenicol (RR 0.79, 0. 66 to 0.94). On this basis and because of the potential toxicity chloramphenicol was not proposed by the applicants for inclusion on the EML. When TMP/SMX was compared to amoxicillin, failure rates were higher for TMP/SMX (RR 1.79, 95%CI 1.13 to 2.84).

For non-severe pneumonia, there was no difference between TMP/SMX versus amoxicillin for cure rate in 2 RCTs (3,468 children; RR 0.99, 95%CI 0.96 to 1.01) (10). Given that amoxicillin is better tolerated with fewer side effects than TMP/SMX argues in favour of including amoxicillin alone on the list. Overall, these data point to beta-lactam regimens as being key part of therapy for CAP in children, similar to what existing evidence suggests for adults.

As noted above, the systematic reviews that were identified provided limited information on superiority. The majority of RCTs included in the reviews were non-inferiority studies but frequently did not meet the criteria for non-inferiority determined by the applicant. The RCTs did not show mortality benefit of adding a flurorquinolone or macrolide to a beta-lactam compared to beta-lactam monotherapy. In children, amoxicillin appeared to be either equivalent or have better cure rates than TMP-SMX. Better tolerability of amoxicillin means it is preferred. There were better cure rates with amoxicillin than cefpodoxime. Given fewer

	clinical failures with ampicillin and gentamicin than chloramphenicol, these would be the preferred choice.
Guidelines (from the application)	Guidelines of the British Thoracic Society (BTS) [26] and the Infectious Diseases Society of America (IDSA) for adults were summarised in the application. Currently available IDSA guidelines (which are being updated) include use of macrolides (either alone or in combination), respiratory fluroroquinolone, beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam), use of anti-pseudomonal 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-betalactamase-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. Furthermore, guidelines recommend doxycycline as an alternative first-line to macrolides as well as ceftriaxone or ampicillin/sulbactam for ICU-patients. 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 (MCA) conducted a review of its existing guidelines for treatment of community acquired pneumonia in children. The review 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 with regard to antibiotic treatment of pneumonia in children: Fast breathing pneumonia: Amoxicillin oral liquid or tablets: at least 40mg/kg/dose twice daily (80mg/kg/day) x 5 days. In areas with low HIV prevalence, oral amoxicillin for 3 days. Severe Pneumonia: First-line: Ampicillin injection 50 mg/kg or benzylpenicillin injection 50 000 units per kg IM/IV every 6 hours for at least five days and gentamicin injection 7.5 mg/kg IM/IV once a day for at least five days. Second-line: Ceftriaxone injection IV. For HIV infected 10 days therapy.
Rationale for antibiotic selection (from the application)	Proposed antibiotics for CAP were based on evidence from systematic reviews and are similar to recommendations in the clinical practice guidelines with the exception of azithromycin which is not proposed for the EML because of concern for safety as reported by the FDA (2). The applicants state that although no systematic review evidence was found for vancomycin, its inclusion for empiric therapy when MRSA is suspected, as suggested by the guidelines was reasonable. In order to minimize the occurrence of antibiotic resistance, and taking into consideration their efficacy, safety, low- cost and availability the applicants proposed the use of amoxicillin, amoxicillin+clavulanic acid, or phenoxymethylpenicillin as first-line empiric (core) therapy for mild to moderate CAP. 'Targeted' antibiotics were defined by the applicants 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 penicillin G, 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.

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	In keeping with a fluroquinolone sparing strategy, use of fluoroquinolones should be reserved for patients with allergies who cannot use beta-lactam and cephalosporins. Caution is needed in the use of fluroquinolones 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 *P. 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: **(eg. additional evidence, dose/duration, costs etc)**	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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 alignment with the WHO guidelines for inclusion on the EMLc. The Committee considered the various antibiotics proposed in the application from the McMaster Group under the guiding principle of parsimony and selected first and second choice antibiotics for this indication for inclusion on the EML. As a result, 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 based on available evidence and are usually narrow spectrum agents.
EML listings: Community acquired pneumonia (CAP) - first and second choice AB **Antibiotics proposed for both EML and EMLc unless specified** **FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc** **FOR ADDITION indicates new antibiotics not currently on EML / EMLc**	

	FIRST CHOICE	SECOND CHOICE
ENDORSEMENT	**Mild to moderate CAP**	
	Amoxicillin	Amoxicillin+clavulanic acid
	Phenoxymethylpenicillin	Doxycycline
	Severe CAP	
	Ceftriaxone or Cefotaxime Clarithromycin	Amoxicillin+clavulanic Clarithromycin
	EMLc: Amoxicillin+clavulanic acid Ceftriaxone or cefotaxime Gentamicin Benzylpenicillin/ampicillin/amoxicillin	

Committee Recommendations:	The Expert Committee endorsed the inclusion of amoxicillin and phenoxymethylpenicillin as first choice therapy options in mild to moderate CAP, and 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 clarithromycin in combination with ceftriaxone or cefotaxime (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 or ceftriaxone or cefotaxime (EMLc) or Gentamicin in combination with benzylpenicillin /ampicillin/amoxicillin (EMLc)] as first choice for severe CAP.

UNCORRECTED VERSION

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UNEDITED VERSION

Pharyngitis

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 is no evidence for antibiotics (1). The major cause of bacterial pharyngitis is Group A Streptococcus (GAS). It is notable that penicillin resistance has yet to be demonstrated by this bacterium, although resistance to macrolides has increased. The major reason to treat GAS other than symptomatic relief has been to reduce complications such as rheumatic fever or post-streptococcal glomerulonephritis.
Summary of evidence: (from the application)	A 2013 Cochrane review of antibiotic therapy for GAS pharyngitis (17 RCTs, 5,352 participants) found no difference in symptom resolution between cephalosporins and penicillin (OR 0.79, 95% CI 0.55 to 1.12) but lower clinical relapse in adults with cephalosporins (OR 0.55, 95% CI 0.31 to 0.99) and no difference between macrolides and penicillin (OR 1.11, 95% CI 0.92 to 1.35) (2) Duration of treatment has also been studied, with the concept 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 (2 to 6 days) with newer agents (including azithromycin and clarithromycin) versus 10 days of penicillin (20 RCTs, 13,102 cases) with the same treatments in children (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 to 0.94). There were no differences in early bacteriologic cure (OR 1.08, 95% CI 0.97 to 1.20) or late clinical recurrence (OR 0.95, 95% CI 0.83 to 1.08). However, there was a significantly greater risk of late bacteriologic recurrence (OR 1.31, 95% CI 1.16 to 1.48) (3). Another Cochrane review (27 trials, 12, 835 participants) that examined complications, reported that antibiotics reduced rheumatic fever (RR 0.27; 95% CI 0.12 to 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 to 0.58), acute sinusitis (RR 0.48; 95% CI 0.08 to 2.76), and peritonsillar abscess within two months (RR 0.15; 95% CI 0.05 to 0.47) compared to those taking placebo. The RCTs demonstrated benefit of using antibiotics for GAS pharyngitis in order to reduce complications, which is of particular relevance in LMICs. Although there is evidence that macrolides and cephalosporins may reduce duration of symptoms this must be weighed against the possibility for resistance against these agents, particularly given the context that penicillin resistance in GAS has never been observed.
Guidelines (from the application)	The Infectious Diseases Society of America *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 recommended penicillin or amoxicillin as the first line agent for GAS pharyngitis. For individuals with serious penicillin allergy, macrolides (azithromycin or clarithromycin) were recommended.

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Rationale for antibiotic selection (from the application)	Pharyngitis frequently has a viral cause - routine practice in some countries is not to treat pharyngitis at all, others typically use a delayed antibiotic prescription policy, and others heavily rely on microbiological testing to support an indication for antibiotic treatment. For Group A Streptococcus, antibiotics can reduce rheumatic fever and suppurative complications. The fact that the evidence suggests similar overall outcomes with penicillin compared to other antibiotic classes, along with the importance of sparing macrolides and cephalosporins argues strongly in favour of penicillin or amoxicillin as first line antibiotics. Clarithromycin can be used where there is a severe allergy to penicillin. It should be noted that routine skin testing for allergy prior to first exposure to penicillins, as is current practise in some regions, is not necessary. For patients with known severe allergies who live in regions with high rates of macrolide resistance, cephalexin would be another option.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The Committee noted that since the vast majority of pharyngitis cases are due to viruses, routine practice in some countries is not to treat pharyngitis at all with antibiotics, others use a delayed antibiotic prescription policy, and others rely on diagnostic tests to support an indication for antibiotic treatment. Antibiotics have indeed limited benefit in streptococcal pharyngitis, except if rheumatic fever is still a problem in a particular setting. The Committee also noted the absence of indication for routine skin testing for allergy prior to first exposure to penicillins. The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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 generally recommended based on available evidence and are usually narrow spectrum agents.
EML listings: Pharyngitis Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR 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 watchful waiting, symptom relief and no antibiotic treatment is the appropriate first-line treatment option for pharyngitis. The Expert Committee endorsed the use of phenoxymethylpenicillin or amoxicillin as first choice therapies for suspected or proven bacterial pharyngitis, and clarithromycin (EML) or cephalexin (EML/EMLc) as second choice therapy for suspected or proven bacterial pharyngitis. The Expert Committee recommended the addition of clarithromycin on the EMLc (with erythromycin as an alternative) as a second choice therapy for suspected or proven bacterial pharyngitis in children.

References:

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UNEDITED VERSION

Sinusitis

Sinusitis	
Applicant(s):	McMaster Group
Introduction: Description of the condition / infecting organisms / public health need?	Most commonly sinusitis is diagnosed and treated in an ambulatory setting and the majority of clinical trials have been conducted in this setting. Patients are typically treated on a clinical basis and typically no attempt is made to obtain cultures for etiologic determination. Given that an estimated >90% of cases of rhinosinusitis are due to viral infections, many of the RCTs have been conducted to test whether antibiotics have any benefit compared to placebo.
Summary of evidence: (from the application)	The question of whether sinusitis actually needs therapy with antibiotics has been addressed in several RCTs. A 2012 Cochrane review (10 RCTs, 2,450 participants) compared antibiotics to placebo for adults with rhinosinusitis and found that purulent secretions resolve faster with antibiotics OR 1.58 (95% CI 1.13 to 2.22) (1). However, 27% of participants versus 15% of those that received placebo experienced adverse events (OR 2.10, 95% CI 1.60 to 2.77). A 2013 Cochrane review of antibiotics for the common cold and purulent rhinitis (11 RCTs, 1,047 participants) reported no difference in terms of cure or persistent symptoms, (RR 0.95 (95% CI 0.59 to 1.51) (2). The RR of adverse effects in the antibiotic group was 1.8 (95% CI 1.01 to 3.21) if initiating antibiotics in patients with symptoms and signs of sinusitis lasting for 7 or more days. However, a more recent review of six RCTs showed a benefit of antibiotic treatment compared to 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 or more days (3). After 10 days however, improvement rates did not differ significantly between patients treated with or without antibiotics (OR 1.36 , 95 % CI 0.66-2.90). In terms of selection of antibiotics, a 2014 Cochrane review (63 RCTs, 1,915 participants) showed that amoxicillin or penicillin were superior to placebo in adults with maxillary sinusitis in terms of clinical failure (RR 0.66, 95%CI 0.47 to 0.94), but also that the risk for clinical failure was higher with cephalosporins or macrolides as compared to amoxicillin/clavulanate (RR 1.37, 95% CI 1.04-1.80) (4). However, cure or improvement were high in both groups (86% for placebo and 91% in antibiotic group). Adverse events were more common in antibiotic than in placebo groups (median of difference between groups 10.5%, range 2% to 23%). The RCTs demonstrate that for sinusitis related to the common cold, which most commonly is caused by rhinovirus, antibiotics offer no benefit over placebo. 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 IDSA guidelines recommend the use of amoxicillin+clavulanic acid as a first line agent and recommend a respiratory fluoroquinolone (levofloxacin or moxifloxacin) or doxycycline (for adults) in patients allergic to beta-lactams (5). Amoxicillin+clavulanic acid as opposed to amoxicillin alone was recommended on the basis of concern that there is an increasing prevalence of *Haemophillus 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 thirteen 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.

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Rationale for antibiotic selection (from the application)	Sinusitis frequently does not require antibiotics, particularly when it is associated with the common cold where they have limited benefit. Delayed prescribing is another strategy to reduce use of antibiotics. The systematic review evidence suggests a higher risk of failure with cephalosporins or macrolides compared to amoxicillin+clavulanic acid. Given the principle of using narrower spectrum agents, amoxicillin alone may be effective, therefore, either amoxicillin or amoxicillin + clavulanic acid were proposed as core choices. Ceftriaxone can be used for severe sinusitis. Fluoroquinolones (levofloxacin, moxifloxacin) should only be used if beta lactams cannot be used.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. As a result, ceftriaxone, levofloxacin and moxifloxacin 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: Sinusitis Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR 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	Amoxicillin	-
	Amoxicillin + clavulanic acid	-

Committee Recommendations:	The Expert Committee noted that watchful waiting, symptom relief and no antibiotic treatment is the appropriate first-line treatment option for sinusitis. The Expert Committee endorsed the inclusion of amoxicillin and amoxicillin + clavulanic acid for suspected bacterial sinusitis as first choice treatment on the EML and EMLc.

References:

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UNEDITED VERSION

Otitis media

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. Avoidance of antibiotics, on the one hand, could lead to reduced resistance, adverse events, and cost, but on the other hand concern has been raised regarding suppurative complications of otitis media if left untreated.
Summary of evidence: (from the application)	A 2015 Cochrane review (13 RCTs, 3,401 children) showed that pain at 24 hours was not reduced by antibiotics after the start of treatment (RR 0.89, 95% CI 0.78 to 1.01) but almost a third fewer had residual pain at two to three days (RR 0.70, 95% CI 0.57 to 0.86) (1). Immediate antibiotics were 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 to 0.76). Antibiotics did not reduce abnormal tympanometry findings at three months (RR 0.97, 95% CI 0.76 to 1.24) nor the number of children with late acute otitis media recurrences (RR 0.93, 95% CI 0.78 to 1.10). Adverse events (such as vomiting, diarrhoea or rash) occurred more often in children taking antibiotics (RR 1.38, 95% CI 1.19 to 1.59). A 2013 Cochrane review (5 RCTs, 1,601 children) showed that one or two daily doses compared with three or four daily doses of amoxicillin with or without clavulanate were comparable for clinical cure at the end of therapy (RR 1.03, 95% CI 0.99 to 1.07), during therapy (RR 1.06, 95% CI 0.85 to 1.33), and at follow-up (RR 1.02, 95% CI 0.95 to 1.09) (2).
Guidelines (from the application)	Guidelines of the American Academy of Pediatrics and Family Physicians and the Canadian Pediatric Society recommend treatment of acute otitis media in children with significant pain for longer than 48 hours and/or fever of 39 degrees or higher (3, 4). The Canadian Pediatric Society guidelines recommend amoxicillin as the antibiotic of choice when it is felt that acute otitis media should be treated with antibiotics [68]. The American Academy of Pediatrics and Family Physicians recommend amoxicillin but suggest amoxicillin/clavulanic acid if a child was previously exposed to amoxicillin in the past 30 days (4). They also recommend cephalosporins for patients with allergy to penicillin (cefdinir, cefuroxime, cefpodoxime, and ceftriaxone).
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, use of amoxicillin and clavulanic acid is another option. Cefuroxime or ceftriaxone can be used for severe cases, minimizing exposure to third generation cephalosporins.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. As a result, ceftriaxone and cefuroxime-axetil were excluded. Recommended first and second choice antibiotics are reported below. The first choice antibiotics are those generally recommended based on available evidence and are usually narrow spectrum agents.

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<table>
<tr><td>EML listings: Otitis media
Antibiotics proposed for both EML and EMLc unless specified

For ENDORSEMENT indicates those antibiotics currently included on EML/EMLc

For ADDITION indicates new antibiotics not currently on EML / EMLc</td><td>
<table>
<tr><td></td><td>FIRST CHOICE</td><td>SECOND CHOICE</td></tr>
<tr><td rowspan="2">ENDORSEMENT</td><td colspan="2">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.</td></tr>
<tr><td>Amoxicillin</td><td>Amoxicillin + clavulanic acid</td></tr>
</table>
</td></tr>
<tr><td>Committee Recommendations:</td><td>The Expert Committee noted that watchful waiting, symptom relief and no antibiotic treatment is the appropriate first-line treatment option for otitis media, unless a child is under 2 years of age with bilateral otitis media.

The Expert Committee endorsed the inclusion of amoxicillin as first choice therapy, and amoxicillin + clavulanic acid as second choice therapy in suspected bacterial otitis media.</td></tr>
</table>

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UNEDITED VERSION

Hospital acquired pneumonia (HAP) & ventilator associated pneumonia (VAP)

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 whose onset begins over 48 hours after admission to hospital. Such patients are often exposed to different regimens of antibiotics with an increased potential to acquire resistant bacteria making antibiotic treatment more challenging. Ventilator associated pneumonia (VAP) is defined by the development of pneumonia while on a ventilator. Typically, the risk of infection with multi-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 anti-pseudomonal 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 (6 RCTs, 1,088 participants) comparing short course to long course antibiotics included no studies on HAP, all patients were mechanically ventilated (1). The authors found a short seven- or eight-day course of antibiotics compared with a prolonged 10- to 15-day course increased antibiotic-free days over the following month and reduced recurrence of VAP due to multi-resistant organisms (one study; N = 110; OR 0.44; 95% CI 0.21 to 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 to 4.16). A 2013 review compared use of linezolid to vancomycin for HAP (9 RCTs, 4,026 participants) (2) They 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, more gastrointestinal side effects were found with linezolid than with vancomycin (RD 0.01, 95% CI 0.00-0.02, p=0.05). For VAP, a 2013 systematic review (4 RCTs) compared short duration (7 to 8 days) of antibiotics to long duration (10 to 15 days) and found 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 in favor of the short-course treatment with a mean difference of 3.40 days (95% CI, 1.43-5.37). There was no difference in relapses between the groups. A 2008 systematic review (41 RCTs, 7,015 patients) compared various antimicrobial regimens for VAP and did not find any differences in mortality when regimens were compared (4). The combination of ceftazidime and an aminoglycoside however was inferior to meropenem (RR 0.70, 95% CI 0.53-0.93) for treatment failure. Rates of mortality when monotherapy was compared to combined therapy 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).

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Guidelines (from the application)	The application reviewed three guidelines, IDSA, NICE, and those of the British Society for Antimicrobial Chemotherapy (5-7). The NICE guidelines recommend that antibiotics for HAP be selected in accordance with local hospital policy (5). A British Society for Antimicrobial Chemotherapy recommends that for early-onset infections (fewer than 5 days following admission to hospital) in patients with not recent exposure to antibiotics and with no risk factors for multi-resistant pathogens to use amoxillin/clavulanate or cefuroxime while for the others cefotaxime or ceftriaxone, a fluroroquinolone, or piperacillin/tazobactam are recommmended (6). For patients with HAP 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 either piperacillin/tazobactam, cefepime, levofloxacin, or a carbapenem (7). Low risk patients with a higher MRSA risk, vancomycin or linezolid should be added, and aztreonam and ceftazidime can be considered for gram negative coverage instead of the antibiotics listed above. For high risk patients or with receipt of intravenous antibiotics during the prior 90 days, empiric double-coverage for gram negatives is recommended, and aminoglycosides are listed as an option in addition to the antibiotics listed above. The recommended duration 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 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 included in this list since it is proposed for the preservation list of those that antibiotics that are last line for highly resistant pathogens. Use of empiric vancomycin should be restricted to suspicion of MRSA. Aminoglycosides are on the list for double pseudomonal coverage if needed. The list includes ceftazidime, cefepime, and piperacillin+tazobactam for anti-pseudomonal coverage. It is recommended that the fluoroquinolones be used only when needed, for example, in the case of a serious allergy. Given the concern about carbapenem resistance, these agents should be used only when there are no other alternatives.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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.

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EML listings: Hospital acquired pneumonia (HAP) Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR 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 Committee reviewed the evidence and limited its recommendation to hospital acquired pneumonia. The Expert Committee did not include antibiotics for VAP in this section due to the condition being relatively rare and the choice of empiric antibiotic treatment in national guidelines being based on local epidemiology/microbiology. The Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid, cefotaxime and ceftriaxone for first choice therapy hospital acquired pneumonia in EML and EMLc. The Expert Committee recommended the addition of Piperacillin + tazobactam for use in hospital acquired pneumonia as one of the first choice therapies in EML and EMLc.

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Sepsis in children

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 the vast majority of cases. The purpose of this chapter is to focus on the empiric 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 (2 RCTs, 127 participants) compared single to combination regimens for suspected early neonatal sepsis, but had indeterminant results on mortality within 28 days (RR 0.75, 0.19 to 2.9) because of the limited sample size (2). A review which examined antibiotic regimens for late onset sepsis in neonates (1 RCT, 24 participants), comparing beta-lactams to beta-lactams and aminoglycosides also was indeterminant (RR 0.17, 0.01 to 0.2) because it was severely underpowered (3).
Guidelines (from the application)	The WHO Department of Maternal, Newborn, Child and Adolescent Health (MCA) conducted a review of its existing guidelines for treatment of sepsis in children and neonates. The review 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 with regard to antibiotic treatment of sepsis in children and neonates: Serious bacterial infection, hospitalized infants with community acquired infection: Gentamicin injection and benzylpenicillin injection 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 cloxacillin oral liquid or tablets for 21 days. Possible severe bacterial infection (PSBI) in young infants where referral is not possible, fast breathing as the only sign of illness: Amoxicillin oral liquid or tablets for 7 days PSBI in young infants where referral is not possible, clinical severe infection: *Option 1:* IM gentamicin injection once daily for 7 days and amoxicillin oral liquid or tablets twice daily for 7 days. *Option 2:* IM gentamicin injection once daily for 2 days and amoxicillin oral liquid or tablets twice daily for 7 days. PSBI, young infants where referral is not possible, critically ill: Ampicillin injection twice daily and gentamicin injection daily for 7 days. For early onset infection, the NICE guidelines suggest use of intravenous benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless local bacterial resistance patterns suggest using a different antibiotic (4). Although not formally a guideline, the American Academy of Pediatrics recommends 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. The WHO handbook recommends, for newborns with any signs of serious bacterial infection or sepsis, to give ampicillin or penicillin and gentamicin as first-line antibiotic treatment (6). This handbook also specifies to consider using cloxacillin and gentamicin if the clinical presentation suggests a higher risk of staphylococcus infection, such as extensive skin pustules, abscess or omphalitis in addition to signs of sepsis.

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Rationale for antibiotic selection (from the application)	The systematic review evidence is extremely limited and essentially does not contribute to deciding which antibiotics should be on the list. The guidelines suggest a penicillin (ampicillin, penicillin, or intravenous benzylpenicillin) along with gentamicin to cover Listeria and gram negatives. As such, these antibiotics were proposed as core agent for neonatal sepsis.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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 alignment 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 based on 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 hram negative bacilli, respectively.
EML listings: Sepsis in children Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc	

	FIRST CHOICE	SECOND CHOICE
ENDORSEMENT	Benzylpenicillin/Ampicillin/Amoxicillin	Ceftriaxone/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 either benzylpenicillin or ampicillin or amoxicillin as the first choice treatment of sepsis in neonates and children, and ceftriaxone or cefotaxime as a second choice therapy for treatment of sepsis in neonates and children. The Expert Committee recommended the addition of amikacin (in combination with cloxacillin) as a second choice option for use in sepsis in neonates and children.

References:

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UNEDITED VERSION

Urinary tract infections (UTI)

Urinary tract infections (UTI)	
Applicant(s):	McMaster Group
Introduction: Description of the condition / infecting organisms / public health need?	Urinary tract infections in the outpatient setting are a common reason for young women in particular to seek medical attention. RCTs have addressed the type and duration of antibiotics in this and other populations. Use of antibiotics for asymptomatic bacteriuria, that is the presence of bacteria in the urine in the absence of symptoms, can drive antibiotic resistance and may also increase the risk for subsequent symptomatic UTIs. While it is accepted practice that asymptomatic bacteriuria should be treated in pregnant women and for men about to undergo urologic procedures, the benefit for therapy in other groups has been questioned and addressed in RCTs.
Summary of evidence: From the application	A 2010 Cochrane systematic review (21 RCTs, 6016 participants) for acute uncomplicated UTIs, found that sulfamethoxazole+trimethoprim (SMX-TMP) was equivalent to fluroroquinolones in achieving short-term (RR 1.00, 95% CI 0.97 to 1.03) and long-term (RR 0.99, 95% CI 0.94 to 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 for nitrofurantoin was similar to that of SMX-TMP (RR 0.99, 95% CI 0.95 to 1.04) as was long-term symptomatic cure (RR 1.01, 95% CI 0.94 to 1.09). For asymptomatic bacteriuria, a 2015 Cochrane review (9 RCTs, 1,61 participants) of RCTs that compared antibiotics to placebo showed that symptomatic UTI (RR 1.11, 95% CI 0.51 to 2.43), complications (RR 0.78, 95% CI 0. 35 to 1.74), and death (RR 0.99, 95% CI 0.70 to 1.41) were similar between the antibiotic and placebo or no treatment arms (2) A 2014 Cochrane review of antibiotics for pyelonephritis in children (27 studies, 4,452 children) reported no significant differences in duration of fever (2 studies, 808 children: MD 2.05 hours, 95% CI -0.84 to 4.94), persistent UTI at 72 hours after commencing therapy (2 studies, 542 children: RR 1.10, 95% CI 0.07 to 17.41) or persistent kidney damage at six to 12 months (4 studies, 943 children: RR 0.82, 95% CI 0.59 to 1.12) between oral antibiotic therapy (10 to 14 days) and intravenous (IV) therapy (3 days) followed by oral therapy (10 days) (3). Similarly, no significant differences in persistent bacteriuria at the end of treatment (4 studies, 305 children: RR 0.78, 95% CI 0.24 to 2.55) or persistent kidney damage (4 studies, 726 children: RR 1.01, 95% CI 0.80 to 1.29) were found between IV therapy (three to four days) followed by oral therapy and IV therapy (seven to 14 days) (3). No significant differences in efficacy were found between daily and thrice daily administration of aminoglycosides (1 study, 179 children, persistent clinical symptoms at three days: RR 1.98, 95% CI 0.37 to 10.53).
Guidelines (from the application)	The IDSA and ESCMID guidelines recommend nitrofurantoin and SMX-TMP for acute uncomplicated cystitis in women (4) Amoxicillin+clavulanate is an alternative choice. Oral fosfomycin is recommended where available due to 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 urinary tract infection, a threshold no longer met for fluroroquinolone in many countries. Amoxicillin+clavulanic acid and SMX-TMP are also recommended for empiric treatment in children aged 2 to 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 (eg, tobramycin or gentamicin) or a third-generation cephalosporin. For pyelonephritis during the first 6 months of life, ceftazidime and ampicillin or an aminoglycoside and ampicillin are recommended. A third generation cephalosporin for children after 6 months of age is recommended for uncomplicated pyelonephritis while ceftazidime and ampicillin or aminoglycoside and ampicillin are suggested for complicated pyelonephritis. Although the guidelines list parenteral as well as oral cephalosporins, in addition to beta-lactams (inlcuding piperacillin, amoxicillin, amoxicillin/clavulanic acid, nitrofurantoin, and aminoglycosides, fluroquinolones are considered second or third line

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	antibiotics for complicated urinary tract infection. The Italian Society of Pediatric Nephrology recommendations are similar (7).
Rationale for antibiotic selection (from the application)	The application summarised the rationale for the proposed EML listings as follows: The systematic review evidence showed that trimethoprim-sulfamethoxazole was equivalent to fluroquinolones for uncomplicated urinary tract infections and that nitrofurantoin was equivalent to trimethoprim-sulfamethoxazole. Therefore, trimethoprim-sulfamethoxazole and nitrofurantoin are listed as core antibiotics. Fluoroquinolones were not included due to the need to preserve this class. Oral fosfomycin is on the list due to minimal resistance and good safety profile. Amoxicillin+clavulanate is on the list for young children while ampicillin and gentamcin are for children with severe illness. Fosfomycin is included as a core antibiotic.
Committee considerations: (eg. additional evidence, dose/duration, cost etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. As a result, ampicillin, fosfomycin, and gentamicin were excluded. Amikacin was preferred to gentamicin because it is usually more frequently active on Enterobacteriaceae, and ciprofloxacin was added as a recommended first line option for empiric treatment in mild-to-moderate pyelonephritis and prostatitis, due to 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 based on available evidence and are usually narrow spectrum agents.
EML listings: UTIs 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	**Pyelonephritis and prostatitis: mild to moderate** Ceftriaxone/Cefotaxime
	Pyelonephritis and prostatitis: severe Ceftriaxone/Cefotaxime	
ADDITION	Amikacin (severe)	N/A

Committee Recommendations:	The Expert Committee endorsed the inclusion of the following medicines as first choice therapies on the EML and EMLc list as follows: • 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 as follows: • Pyelonephritis or prostatitis - mild to moderate: ceftriaxone or cefotaxime The Expert Committee recommended the addition of amikacin (in combination with ceftriaxone or cefotaxime) for severe pyelonephritis or prostatitis on the EML and EMLc for UTIs.

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UNEDITED VERSION

Meningitis

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, RCT evidence is limited and recommendations for antimicrobials are driven largely on susceptibility patterns of the most common pathogens along with experimental work in animal models.
Summary of evidence: (from the application)	In a 2015 systematic review, chloramphenicol was compared to other antibiotics (2 penicillins, 2 cephalosporins, and 1 tetracycline) (5 RCTs, 1,753 patients) (1). Chloramphenicol was associated with higher mortality than other antibiotics (RR 1.27, 95% CI 1.00-1.60). In contrast, an older 2007 Cochrane review (19 RCTs, 1496 patients) that compared third generation cephalosporins to treatment with penicillin or ampicillin-chloramphenicol found no difference for death (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%)[138]. There was a reduced risk of culture positivity of CSF after 10 to 48 hours (RD -6%; 95% CI -11% to 0%) and an increase in the risk of diarrhoea between the groups (RD 8%; 95% CI 3% to 13%) with third generation cephalosporins versus penicillin/ampicillin-chloramphenicol (2). A 2009 systematic review compared short course (4 to 7 days) to long-course (7 to 14 days) of antibiotics in children (5 RCTs 426 patients) and found no difference in clinical success (OR 1.24, 95% CI 0.73 to 2.11), long-term neurological complications (OR 0.60, 95% CI 0.29 to 1.27) or long-term hearing impairment (OR 0.59, 95% CI 0.28 to 1.23) (3).
Guidelines (from the application)	The NICE guidelines recommend ceftriaxone for patients aged 3 months and older while those younger should be treated with intravenous cefotaxime along with amoxicillin or ampicillin (4). They also recommend that vancomycin should be added for those who have received prolonged or multiple exposure to antibiotics (within past 3 months) and for those with travel outside of the UK. IDSA guidelines recommend ampicillin and cefotaxime or an aminoglycoside for children less than one month of age, vancomycin and ceftriaxone or cefotaxime for children older than 23 months to adults 50 years of age, and recommend adding ampicillin for those over 50 years for coverage of *Listeria monocytogenes* (5). Vancomycin along with either cefepime, ceftazidime, or meropenem is recommended for patients with penetrating trauma, who are post-neurosurgery, or who 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, as such, it was 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: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. As a result, ceftazidime, amikacin, gentamicin and vancomycin were excluded, because the Committee considered that these antibiotics have no or limited 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 based on available evidence and are usually narrow spectrum agents.

EML listings: acute bacterial meningitis Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc	

	FIRST CHOICE	SECOND CHOICE
ENDORSEMENT	Ceftriaxone/Cefotaxime	Ampicillin/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 options for use in suspected acute bacterial meningitis; and chloramphenicol, benzylpenicillin, ampicillin or amoxicillin as second choice therapies, recognising that the latter 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 Expert Committee recommended the addition of meropenem to the EMLc for use in neonatal meningitis 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

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 viscus 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 hematogenous dissemination (e.g. spontaneous bacterial peritonitis in the absence of an underlying infection of the viscus), usually in the setting of an immunocompromised state, or dialysis-related infections.
Summary of evidence: (from the application)	Five systematic reviews were included (1-6). In a 2005 review (6), 40 studies (5,094 patients) were evaluated to compare the efficacy of various antibiotics for secondary peritonitis, i.e. infection of the visceral organ that extends beyond the organ, e.g. complicated appendicitis or cholecystitis. 38 of the 40 studies compared two regimens of antibiotics and 2 studies compared 3 regimens. The antibiotics evaluated included carbapenems (meropenem or imipenem), as single agents compared to each other or to cephalosporin and metronidazole combination or to piperacillin+tazobactam, regimens of clindamycin and an aminoglycoside (gentamicin or amikacin or tobramycin) compared to 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 to others with very large confidence intervals, though: OR 2.03, 95% CI 0.88 to 4.71 and OR 1.51, 95% CI 0.66- 3.43 respectively. However, aminoglycoside-based regimens were shown to be inferior against all comparators available in terms of clinical success (OR 0.65, 95% CI 0.46-0.92). When broad spectrum beta-lactams were compared to 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 to others, 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) nor for clinical success (OR 1.25, 95% CI 0.57-2.74). Similarly for cephalosporin and anti-anaerobe regimens versus others, no difference in infection related death (OR 5.45, 95% CI 0.25-116.63) nor for clinical success (OR 0.71, 95% CI 0.29 to 1.75) was observed. However, the group of cephalosporins and beta-lactams were found to be superior in terms of clinical success compared 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 groups had been compared to one specific other antibiotic group, no firm conclusions can be drawn from this evidence. It is possible that an outlier antibiotic group (e.g. aminoglycoside-based antibiotics as in Wong et al. (6)) 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-lactam. In a systematic review and meta-analysis comparing ertapenem to ceftriaxone (eight RCTs, 2,883 patients), similar clinical success was reported OR 1.13, 95% CI 0.75 to 1.71. A comparison of moxifloxacin to other antibiotics (4 RCTs, 2,444 patients), showed similar effects for clinical cure (OR 0.80, 95% CI 0.61-1.04) and mortality (OR 0.91, 95% CI 0.45-1.83); more adverse events were observed in the moxifloxacin group (OR 1.33, 95% CI 1.07-1.63), however, the overall incidence of serious adverse events was similar (OR 1.23, 95% CI 0.59-2.60) (4). A review comparing ertapenem to piperacillin+tazobactam (6 RCTs, 3,161 patients) showed no difference in clinical success (OR 1.15, 95% CI 0.89-1.49) (1). In an older systematic review (3), ciprofloxacin plus metronidazole was found to be superior in terms of clinical cure than beta-

	lactam based antibiotics (OR 1.69, 95% CI 1.20-2.30), however, the studies on which this observations had been based were conducted prior to the recent increase in fluoroquinolone resistance. Tigecycline, a tetracycline derivate and the first glycylcycline, received a black box warning and the FDA recommends against its use unless no other better alternative agents are available. However, if the higher mortality was due to a lower efficacy of the drug, one would expect lower cure rates, which was not the case in the systematic review by Shen et al. 2015 (5), who did not find a difference in clinical and microbiological cure as compared to imipenem or ceftriaxone plus metronidazole. In summary, for most comparisons, the precision in the summary estimates is very wide, and none met our definition of non-inferiority, thus, a clinically significant difference cannot be ruled out. Furthermore, the review of the clinical trial evidence does not point to superior of single agents or combination regimens. When we found statistically significant differences, these were obtained by aggregating several antibiotics groups at the expense of capacity to identify discrete antibiotics determining better effects.
Guidelines **(from the application)**	Two guidelines were considered relevant for this review (7, 8). The IDSA guideline (7), summarized recommendations for empiric therapy. A very comprehensive approach in terms of antibiotic choices had been used in this CPG, ending to recommend a large list of antibiotics which includes several overlapping agents. This approach differs from the parsimony approach of the essential medicines list. 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-clavulanate), or advanced-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime) plus metronidazole. With severe beta-lactam allergies, either an aminoglycoside or ciprofloxacin plus metronidazole are recommended. Single-agent empiric therapy for adults with mild to moderate severity included cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic acid. For high risk or severely ill adults, imipenem, meropenem, doripenem, and piperacillin+tazobactam were recommended. Recommended combination regimens include a cephalosporin (cefazolin, cefuroxime, ceftriaxone, cefotaxime, 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) each in combination with metronidazole are recommended. The guidelines also make recommendations for empiric therapy for health care-associated complicated intra-abdominal infections. If ESBL-producing Enterobacteriaceae are amongst the most common pathogens involved in this type of infections locally, then regimens including a carbapenem and aminoglycosides, but not cephalosporins are recommended. Ceftazidime is not recommended where > 20% P. aeruginosa are resistant. Vancomycin is recommended in addition to other antibiotics when coverage for MRSA is needed based on the local antibiogram. For the empiric therapy of acute cholecystitis, cefazolin, cefuroxime, or ceftriaxone is recommended for mild to moderately severe community acquired infection. A carbapenem (imipenem, meropenem, doripenem), piperacillin-tazobactam, a fluoroquinolone (levofloxacin or ciprofloxacin), or cefepime, each in combination with metronidazole is recommended for severe community acquired cholecystitis. For acute cholangitis following bilio-enteric anastomosis, or for healthcare 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 due to high resistance rates amongst E. coli, and against the use of

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	cefotetan and clindamycin because of resistance in the Bacteroides fragilis group, aminoglycosides in non-severe, non-hospital-acquired cases, and recommends caution when using fluoroquinolones because of increasing resistance rates. In contrast to the IDSA guidelines, the World Society of Emergency Surgery (WSES) guidelines (8) recommend either amoxicillin-clavulanate or ciprofloxaxin and metronidazole for extra-biliary or biliary acute intra-abdominal infection in patients that are not critically ill who have no risk factors for ESBL. 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 intrabiliary disease. Where there is an increased risk of ESBL, meropenem or imipenem with the option of adding fluconazole for extrabiliary disease and piperacillin and tigecycline for intra-biliary disease with the option of fluconazole are listed. For hospital acquired intrabdominal infection in the absence of critical illness where there is a risk for a multi-drug resistant organism, the guidelines recommend piperacillin, tigecycline, and fluconazole. For hospital-acquired infection in a critically ill patient, piperacillin, tigecycline, an echinocandin (caspofungin or anidulofungin, or micafungin) or a carbapenem (meropenem, imipenem, doripenem), teicoplanin, and an echinocandin (caspofungin or anidulofungin, or micafungin) are recommended.
Rationale for antibiotic selection **(from the application)**	Since the overview of systematic reviews yielded indeterminate findings, the application's proposals for the EML are based on 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 PO/IV or a cephalosporin (cefotaxime and ceftriaxone) with metronidazole fulfil the curative as well as the resistance preservative intent. For hospital-acquired or severe cases, the same cephalosporins with metronidazole can be used, or piperacillin+tazobactam instead of amoxicillin+clavulanic acid. Fluoroquinolones should be considered second line for patients who have contraindications to betalactams/cephalosporins due to resistance concerns, and concerns about potential harm. Of the fluoroquinolones, moxifloxacin has not been added to the list despite recommendations in one guideline due to the availability of many other options and given the signal for higher adverse event rates. Vancomycin should be used for patients with concerns about a MRSA infection. Teicoplanin was not proposed due to redundancy and several indications for vancomycin across all syndromes. Ceftazidime, meropenem, and the aminoglycosides are listed as targeted antibiotics based on local resistance data as alternative options to the core antibiotics. Ampicillin can be considered if additional enterococcal coverage is needed if the used regimen would otherwise not be covering enterococcus (e.g. ceftriaxone/metronidazole). Of the antibiotics listed in the guidelines, cefazolin, cefoxitin and cefuroxime were excluded for redundancy, as ceftriaxone is listed which also offers broader gram-negative coverage. Also excluded were ticarcillin-clavulanate and piperacillin, as piperacillin+tazobactam is considered more appropriate and is listed for several syndromes. Tigecycline has a potential role as a niche or last resort antibiotic for multi-resistant pathogens or if all first- and second line antibiotics cannot be used, but was not considered as a core or targeted antibiotic due to the black box warning by the FDA related to the presumed higher mortality rate. Cefepime was not proposed as it was felt to be redundant with the antibiotics already listed above, and the potential concern about inferiority in terms of mortality (see chapter in immunocompromised hosts). Ampicillin-sulbactam, cefotetan, and clindamycin were not proposed as their use is discouraged in the IDSA guideline due to resistance concerns.

	Ertapenem was proposed for the reserved list as it is considered a niche antibiotic, in particular for patients with suspected ESBL when *P. aeruginosa* coverage is not needed. The applicants proposed only listing meropenem of the available carbapenems as it is the most frequently recommended carbapenem across all syndromes, therefore imipenem and doripenem were excluded.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. As a result, levofloxacin, ampicillin, ceftazidime, gentamicin, tobramycin and vancomycin were excluded. Ceftazidime, gentamicin, tobramycin and vancomycin have limited indications in community-acquired complicated intra-abdominal infections. Ampicillin only provides enterococcal coverage, which is usually not needed for mild-to-moderate complicated intra-abdominal infections. Ciprofloxacin was preferred over levofloxacin (for parsimony, and to preserve levofloxacin as a treatment for multi-drug resistant tuberculosis). Recommended first and second 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: complicated intra-abdminal infections Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc	

	FIRST CHOICE	SECOND CHOICE
ENDORSEMENT	**Mild to moderate:** Amoxicillin + clavulanic acid Ceftriaxone/Cefotaxime in combination with Metronidazole	Ciprofloxacin in combination with Metronidazole
	Severe Ceftriaxone/Cefotaxime in combination with Metronidazole	
ADDITION	**Severe** Piperacillin-Tazobactam	**Severe** 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/cefotaxime in combination with metronidazole] as first choice therapy, and ciprofloxacin in combination with metronidazole as second choice therapy • Severe: ceftriaxone/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 & soft tissue infections (including cellulitis and surgical site infections)

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 where the host is healthy, including cellulitis, erysipelas, human and animal bites, or 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. In this section we also include surgical site infections 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 to vancomycin, such as linezolid and daptomycin, for infections that would be caused by MRSA. In a 2014 systematic review and meta-analysis, six RCTs (1,710 patients) compared daptomycin to other antibiotics (1).Clinical success was similar when daptomycin was compared to vancomycin (4 RCTs) (OR 1.19, 95%CI 0.77-1.83) or to a penicillase-resistant penicillin (2 RCTs), OR 1.05, 95%CI 0.84 to 1.31. A difficulty in the interpretation of this review is that RCTs of both complicated and uncomplicated skin and soft tissue infection were included. Similarly, no superiority was found for daptomycin in another systematic review that included 3 RCTs, 1557 patients with an OR of 0.89 (95% CI 0.63, 1.25) for clinical success as compared to semi-synthetic penicillins (5). Several SRs compared linezolid to vancomycin and other antibiotics (2, 4, 6, 10-12). The comparison by Falagas et al. including 12 RCTs and 6,093 patients showed superiority of linezolid in terms of clinical success with an OR of 1.67 (95% CI 1.31-2.12) (6). They concluded, however, that the use of less potent anti-staphylococcal beta-lactams in the comparator groups such as cefriaxone, the same all-cause mortality, and the higher probability of thrombocytopenia in the linezolid group, should be taken into account and may limit the use of linezolid to specific patient populations or infections that are difficult to treat with other antibiotics. A 2013 Cochrane review compared linezolid to vancomycin for skin and soft tissue infection (9 RCTs, 3,144 patients) (2). Again, linezolid was associated with a significantly better clinical (RR 1.09, 95% CI 1.03 to 1.16) and microbiological cure rate in adults (RR 1.08, 95% CI 1.01 to 1.16) than vancomycin. There were fewer incidents of red man syndrome (RR 0.04, 95% CI 0.01 to 0.29), pruritus (RR 0.36, 95% CI 0.17 to 0.75) and rash (RR 0.27, 95% CI 0.12 to 0.58) in the linezolid group compared with vancomycin, however, more people reported thrombocytopenia (RR 13.06, 95% CI 1.72 to 99.22), and nausea (RR 2.45, 95% CI 1.52 to 3.94) when treated with linezolid. The 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 also compared linezolid to vancomycin (9 RCTs, 2489 patients) for the treatment of gram positive infections, including skin and soft tissue infections (10). Linezolid appeared to have higher efficacy than vancomycin in patients with skin and soft-tissue infections (OR 1.40, 95% CI 1.01-1.95). One systematic review to compare linezolid to vancomycin for MRSA skin and soft tissue infections included only 1 RCT of 59 patients and concluded better efficacy with linezolid than vancomycin (RR 1.80, 95%CI 1.20 to 2.68) (11). Another review also found superiority of linezolid in 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, another review compared linezolid to vancomycin for MRSA skin and soft tissue

	infections in hospital inpatients (4 RCTs, 174 patients) and found no significant difference in clinical cure between the groups although the point estimate was in favour of linezolid (RR 2.94; 95% CI 0.35-25) (12). A Cochrane SR focussing on diabetic foot infections including 20 RCTs with 3,791 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 the vast majority of comparisons were very wide and could as such not rule out a potentially clinically significant difference. The only comparisons that yielded significant differences were comparisons of imipenem versus piperacillin+tazobactam and piperacillin plus clindamycin, where more adverse events were noted in the comparator groups (RR 3.5, 95% CI 1.56-7.86, and RR 3.70, 1.19-11.11, respectively). A systematic review comparing beta-lactam antibiotics to macrolides or lincosamide in patients with cellulitis or erysipelas (15 RCTs, 462 patients for clinical cure, and 3,032 for adverse event outcomes), reported similar clinical cure between the 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, 2,488 patients, macrolides and streptogramins were found to be more effective than penicillin, RR 0.84, 95%CI 0.73 to 0.98 (8). A Cochrane review of impetigo reported that, for oral therapy in 2 RCTs of a total of 79 patients, penicillin was inferior to erythromycin for cure rates, RR 1.29, 95%CI 1.07 to 1.56 and inferior to cloxacillin in 2 RCTs of 166 participants (RR 1.15, 95%CI 1.01 to 1.32) (9). In summary, several SRs reported higher cure rates with linezolid as compared to 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 undetermined, thus, no conclusions could be drawn. Penicillin was shown to be inferior to erythromycin and cloxacillin for treatment of impetigo.
Guidelines **(from the application)**	The 2014 IDSA guidelines on skin and soft tissue infections (13) that covers paediatric as well as adult patients recommend the following oral options for treatment of impetigo: dicloxacillin, cephalexin, erythromycin, clindamycin, and amoxicillin-clavulanate. For purulent skin and soft tissue infections (most likely due to *S. aureus*), recommendations include (dicl)oxacillin, cefazolin, clindamycin, cephalexin, 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, either penicillin G or V, clindamycin, nafcillin, cefazolin, or cephalexin can be used with the latter two specifically recommended for non-Type 1 penicillin-allergy. For necrotizing infections of the skin, fascia, and muscle, the IDSA guideline recommend piperacillin-tazobactam and vancomycin, a carbapenem (meropenem, imipenem, ertapenem), or cefotaxime and metronidazole or clindamycin. Antibiotics including penicillin G, semi-synthetic penicillins (naficillin, oxacillin), cefazolin, vancomycin, clindamycin, doxycycline, ceftriaxone, as well as daptomycin, quinupristin/dalfopristin, and linezolid, are listed as options for specific pathogens such as Streptococcus, S.aureus, Clostridium species, Aeromonas hydrophila, and Vibrio infections. For animal bites, amoxicillin+clavulanate is recommended as oral therapy. For intravenous 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-clavulanate and ampicillin-sulbactam should be used. Carbapenems and doxycycline are also listed as alternatives. Vancomycin, daptomycin, linezolid, and colistin are agents that can be used in the presence of

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	selective multi-resistant bacteria. For incisional surgical site infections of the intestinal or genitourinary tract, ticarcillin-clavulanate, pipercillin-tazobactam, carbapenems (imipenem, meropenem, and 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, cephalexin, trimethoprim-sulfamethoxazole, and vancomycin are suggested. For surgery of the axilla or perineum, either ceftriaxone or a fluoroquinolone (ciprofloxacin or levofloxacin) in combination with metronidazole are recommended. Other than the usual recommendation not to use certain antibiotics in young children if it can be avoided (fluoroquinolones, doxycycline), the recommendations did not vary depending on age of the patients. The 2012 IDSA guidelines specific for diabetic wound infections (14) recommend that clinically uninfected wounds do not get treated with antibiotics, and that, if infected, antibiotic treatment should be supported by debridement as needed as well as wound care. For mild infections, the following antibiotics are listed as potential options: dicloxacillin, clindamycin, cephalexin, levofloxacin, amoxicillin-clavulanate, 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 with clindamycin, imipenem-cilastatin. For (potential) MRSA infections, linezolid, daptomycin, or vancomycin. For (potential) P. aeruginosa infections, piperacillin/tazobactam is recommended. Other options listed for P. aeruginosa are: ceftazidime, cefepime, aztreonam, and carbapenems.
Rationale for antibiotic selection **(from the application)**	Amoxicillin+clavulanate, dicloxacillin, cefuroxime and cephalexin are recommended in the guidelines and all provide appropriate gram-positive coverage as needed for treatment for mild skin- and soft-tissue infections and bites. For moderate to severe infections, intravenous antibiotics are listed as core antibiotics that also provide appropriate gram-positive coverage, and if needed depending on the choice within this group, gram-negative and anaerobic coverage (see table). Metronidazole is also listed as a core antibiotic if combined with another antibiotic with no anaerobic coverage when anaerobes are a consideration (e.g. abscesses). Clindamycin is listed as a targeted antibiotic for mild infections as an alternative agent if MRSA coverage is deemed to be needed, but as a core antibiotic for necrotizing fasciitis in the table for moderate to severe infections. Other options if MRSA coverage is needed is doxycyclin and TMP/SMX, as well as vancomycin when intravenous treatment is needed, which are all listed as targeted antibiotics. Piperacillin/tazobactam is listed as 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), as is meropenem as another alternative if even broader gram-negative coverage is needed. The fluoroquinolones should only be used if no other option is available due to the potential harm and resistance associated with this group of antibiotics, and are therefore listed as targeted antibiotics. Linezolid, although shown based on data from RCTs to be superior to vancomycin and/or beta-lactams, was not included in the core or targeted antibiotic list due to several concerns. First, as outlined by Falagas et al., the beta-lactam comparators in many RCTs were not optimal anti-staphylococcal beta-lactams. Furthermore, there was no significant effect on mortality, and the safety profile of linezolid is inferior due to the much higher risk of thrombocytopenia, which requires monitoring and has the potential of severe adverse event associated with prolonged hospitalization, platelet transfusion and intensive care unit admission. Therefore, linezolid is considered a niche antibiotic for patient population in which the other options cannot be used or failed, and is as such listed as a conserved antibiotic. Although being listed in CPGs as potential options for treatment, daptomycin and quinupristin/dalfopristin were not included due to the lack of data showing any benefit over well-established treatment options listed below. Daptomycin can be considered as an alternative for intravenous MRSA coverage

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	if vancomycin cannot be used and has several other niche indications in other syndromes, and was as such added to the list of conserved antibiotics. Penicillin is not recommended for treatment of impetigo based on guidelines and SR data. Nafcillin was not added as the IDSA guideline state that it is less convenient than cefazolin, and due to the risk of bone marrow suppression. Despite being listed in the IDSA guidelines, erythromycin is not included due to the concerns raised in the guidelines around resistance in S. aureus and S. pyogenes. Colistin is listed on the conserved list as it should only be used when no other options are available. Cefepime was not added as it was considered to be redundant with the antibiotics already listed below, and the potential concern about inferiority in terms of mortality (see chapter febrile neutropenia). Aminoglycosides, tigecyclin, ceftaroline, aminoglycosides, ceftazidime, and aztreonam are not considered for listing for skin and soft tissue infections due to redundancy as there are other options that are listed for several other indications (e.g. vancomycin for MRSA, meropenem and piperacillin/tazobactam with broad spectrum against gram-negatives including P. aeruginosa), however, cefepime, aztreonam and tigecyclin are listed on the conserved list for other syndromes. The applicant did not list ampicillin-sulbactam and ticarcillin-clavulanate due to redundancy with other beta-lactams listed (amoxicillin-clavulanate and piperacillin-tazobactam). Ertapenem is listed as a conserved antibiotic as a niche product e.g. if empiric ESBL coverage is needed, and imipenem-cilastatin was not considered due to redundancy with meropenem with the latter being listed for many more syndromes. Meropenem as well as piperacillin+tazobactam should only be used if there is a concern for infection by gram negatives resistant to other betalactam/cephalosporins listed.
Committee considerations: **(eg. additional evidence, dose/duration, costs etc)**	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. 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 listed in the application for severe skin and soft tissue infections were excluded, since the Committee focussed on the empiric treatment of common mild to moderate community-acquired infections. The Committee listed amoxicillin + clavulanic acid and cloxacillin for parsimony reasons, in particular 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 provides also good coverage for bites. The Committee listed cloxacillin, but noted that any IV anti-staphylococcal penicillin is appropriate. For oral administration, cloxacillin, dicloxacillin and flucloxacillin are preferred due to better bioavailability. Recommended first and second choice antibiotics are reported below.

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EML Listings: skin and soft tissue infections Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc		FIRST CHOICE	SECOND CHOICE
	ENDORSEMENT	Amoxicillin + clavulanic acid	Cefalexin
		Cloxacillin	
	ADDITION	N/A	
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

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 a normal 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, where therapy is typically empiric, or cause-specific such as cholera in epidemic settings. In this section, the focus is on empiric use, in keeping with the other sections where 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. Given increasing resistance rates, the risk for superinfection, and harm due to shiga-toxin producing organisms that can be triggered by antibiotic exposure, the potential benefits of antibiotics need to be weighted against these potential risks. Empirical treatment is usually considered in the case of febrile traveler's diarrhoea. In non-travel related diarrhoea, empiric treatment should only be considered with severe/invasive disease. The following summary considers the acute infectious diarrhoea syndrome review 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 aimed to assess the effect of oral antibiotics for traveller's diarrhoea.(1) There were 12 RCTs identified showing a greater cure by 72 hours when any antibiotics were used compared to placebo (OR 5.90, 95% CI 4.06 to 8.57). Persons who took antibiotics experienced more side effects than those taking placebo (OR 2.37, 95% CI 1.50 to 3.75). Antibiotics reviewed included fluoroquinolones, trimethoprim-sulfamethoxazole, ampicillin, azithromycin, aztreonam, bicozamycin, furazolidone, pivmecillinam, and trimethoprim alone. Although the authors had planned an analysis to compare different antibiotics, this was not carried out because of concerns that there was significant publication bias, therefore, this evidence cannot be used to prioritize one antibiotic over the other. A Cochrane review in patients with cholera (39 RCTs or quasi-experimental studies, 4,623 participants) confirmed that antibiotics reduce the duration of diarrhoea and stool volume as compared to placebo or no treatment, however, there was a long list of antibiotics considered in the active treatment arm (tetracycline, doxycycline, norfloxacin, trimethoprim-sulfamethoxazole, azithromycin, erythromycin, chloramphenicol, ciprofloxacin, furazolidone, pivmecillinam), thus, no conclusions on the efficacy of specific drug classes could be made.(2) The authors also provided head to head comparisons in duration of diarrhoea and clinical cure. Duration of diarrhoea was shorter by over a day 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 (RR 0.32, 95% CI .23-0.44), too. Furthermore, tetracycline was found to be superior to trimethoprim-sulfamethoxazole (RR 0.56, 95% CI 0.34-0.92 for clinical failure). A Cochrane review assessed antibiotics for non-typhoidal Salmonella infection (12 RCTs, 767 participants), concluding that there was a lack of benefit for antibiotics but did not compare various antibiotics.(3) Only microbiological cure was significantly better with fluoroquinolones as compared to placebo (RR 0.33, 95% CI 0.20 to 0.56), but this did not translate into a benefit in clinically important outcomes. Another Cochrane review identified RCTs for treating *Shigella* dysentery.(4) The review concluded that there was insufficient evidence to consider any class of antibiotic superior for treating *Shigella* dysentery. Fluoroquinolones were compared to beta-lactams in 6 RCTs with no significant difference, but in trials where >90% of participants

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	had confirmed Shigella, beta-lactams were more effective than fluoroquinolones (RR 4.68, 95% CI 1.74 to 12.59). Two trials compared fluoroquinolones to macrolides and two compared co-trimoxazole to beta-lactams, and both comparisons showed no difference between groups. Single trials of trimethoprim-sulfamethoxazole versus furazolidone, oral gentamicin versus nalidixic acid, sulphonamides versus tetracyclines showed no significant differences. The confidence intervals around the risk estimates were very wide, however, therefore, a potentially patient-relevant difference between these antibiotics cannot be ruled out. The evidence is extremely limited for either empiric therapy of traveller's diarrhoea or for laboratory confirmed diarrhoeal infection in low and middle income countries, and no data could be found favoring one antibiotic over the other. Thus, recommendations are based on guidelines (see below). The exception is that for confirmed Shigella dysentery, beta-lactams appear to be superior to fluoroquinolones. For cholera, there is evidence that azithromycin is superior to fluoroquinolones. Also, trimethoprim-sulfamethoxazole 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 empiric treatment. The 2001 IDSA guidelines recommended fluoroquinolones for adults and trimethoprim-sulfamethoxazole for children for traveller's diarrhoea.(5) A caveat is warranted, however, given the increase in rates of fluoroquinolone-resistant Campylobacter infections. Also, patients with enterohemorrhagic *E. coli* infections should not be treated with antibiotics due to the higher risk of hemolytic uremic 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 severe or if the patient is <6 months or >50 years old or has prostheses, valvular heart disease, severe atherosclerosis, malignancy, or uremia, trimethoprim+sulfamethoxazole (if susceptible), a fluoroquinolone or ceftriaxone is recommended. For Shigella, trimethoprim-sulfamethoxazole, a fluoroquinolone, nalidixic acid, ceftriaxone, and azithromycin are choices. The NICE guidelines for children < 5 years recommend antibiotics in this age group only if there is suspected bacteremia, 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 for traveller's diarrhoea only when the likelihood of bacterial pathogens is high enough to justify the potential adverse effects of antibiotics.(7) These guidelines recommed a fluoroquinolone, azithromycin, or rifaximin. For *C. difficile* infections, metronidazole and oral vancomycin are recommeneded.(8) The WHO Department of Maternal, Newborn, Child and Adolescent Health (MCA) conducted a review of its existing guidelines for treatment of dysentery (shigellosis) and cholera in children. The reviews were informed by systematic literature reviews 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 dysentery and cholera: *Dysentery:* 1st line: Ciprofloxacin oral liquid or tablets 15mg/kg twice daily for 3 days. 2nd line: IV/IM ceftriaxone injection 50-100mg/kg for 2-5 days ('to be used only when local strains of Shigella are known to be resistant to ciprofloxacin). Alternative 2nd line drugs: Azithromycin oral liquid or capsules 12mg/kg on day 1; then 6mg/kg on day 2-4 (total course: 4 days) or cefixime oral liquid or tablets, 8 mg / kg / day. *Cholera:*

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	Doxycycline oral liquid or tablets 4 mg / kg as a single dose or erythromycin oral liquid or tablets 12.5mg/kg four times daily for 3 days or ciprofloxacin oral liquid or tablets – 10-20mg/kg/dose x 2 times x 5 days or azithromycin oral liquid or capsules 20mg/kg as a single dose (only in epidemics). In non-epidemic situations, antibiotics should only be used for children with severe dehydration.
Rationale for antibiotic selection (from the application)	For travellers diarrhoea, trimethoprim+sulfamethoxazole was listed as a core antibiotic for both, children and adults, if treatment is deemed necessary. Azithromycin and fluoroquinolones, although listed as alternatives in the guidelines, should only be used if no other more appropriate options are available due to resistance concerns as well as potential harm. Ceftriaxone was listed as a core antibiotic given the superiority of beta-lactams for treatment of confirmed Shigella dystentery. For cholera, azithromycin should be considered first line treatment given 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 nalidix acid were not proposed due to redunancy, with other fluoroquinolones proposed for several more indications across all syndromes. Rifaximin was not included based on redundancy with other options available that are relevant for other indications as well. Chloramphenicol is proposed for the preserved list as a last resort option for typhoid fever if no other antibiotics are available based on recommendation from experts from low and middle income countries on the advisory panel. Based on the data from systematic reviews, trimethoprim+sulfamethoxazole, ciprofloxacin, and erythromycin are not recommended for treatment of cholera.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for allergy were not considered. The 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 this indication for inclusion on the EML and/or EMLc. As a result, levofloxacin and erythromycin were excluded. Ciprofloxacin was preferred over levofloxacin (for parsimony, and to preserve levofloxacin as a treatment for multi-drug resistant tuberculosis). Recommended first and second 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 FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc	

	FIRST CHOICE	SECOND CHOICE
	In most circumstances of 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 diarrhea/ dysentery** Ciprofloxacin	Ceftriaxone Cefixime Azithromycin Sulfamethoxazole + trimethoprim
	Cholera Azithromycin (EMLc) Doxycycline (EML)	Ciprofloxacin Doxycycline (EMLc)
	C. difficile infection:	
	Metronidazole	
ADDITION		Vancomycin (oral) – C. difficile

Committee Recommendations:	The Expert Committee noted that In most circumstances of non-bloody and non-febrile presentations, 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 therapy. The latter should be used only in severe/life threatening conditions • C. difficile infection: metronidazole as first choice therapy The Expert Committee recommended the addition of vancomycin (oral) for C.difficile infection as a second choice therapy.

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Sexually transmitted infections

Sexually transmitted infections (STIs)	
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 for this section is sexually transmitted infections. The McMaster application targeted comparative empiric therapy, or comparative antimicrobials for Gonococcus and Chlamydia trachomatis, the two most common pathogens for infectious urethritis. Furthermore, syphilis was 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 present a major burden of disease worldwide and negatively affect people's 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)	McMaster Group: For treatment of urethritis by *C. trachomatis*, one review compared azithromycin to doxycycline (23 RCTs, 2,384 participants) and reported a non-significant summary estimate in favour of doxycycline (absolute risk benefit 1.5% (95% CI -0.1% to 3.1%)).(1) An earlier review (12 RCTs, 1543 participants) also reported no difference between these two antibiotics for microbiologic cure rates (risk difference 0.01; 95% CI, -0.01 to -0.02%). (2) However, another SR by the same first author found that clinical cure had decreased significantly in more recent studies since 2009 (67%) compared to prior to 2009 (85%), which is questioning how useful azithromycin is nowadays given the increase in resistance rates observed.(3) The potential risk benefit of doxycycline and the reduction in clinical cure rates in more recent studies with azithromycin support the use of doxycycline. This was confirmed by a recent non-inferiority trial that reported that failure rates (none in the doxycycline group and 5 in the azithromycin group) exceeded the margin for non-inferiority and therefore non-inferiority was not established.(4) On the other hand, if adherence to a multiple day regimen is a concern, azithromycin still appears to be the best choice. A review of single-dose azithromycin versus erythromycin plus amoxicillin for *C. trachomatis* infection during pregnancy (8 RCTs, 587 participants) found no difference in treatment success between the two groups (OR 1.46, 95% CI 0.56 to 3.78).(5) Azithromycin was found to have fewer adverse events than erythromycin (OR 0.11, 95% CI 0.07-0.18), therefore, erythromycin is not an ideal treatment given its weak benefit-to-harm balance for this indication. Two systematic reviews comparing azithromycin to benzathine penicillin for syphilis were identified (6, 7). While no difference had been identified in the newer review (3 RCTs) but with confidence intervals exceeding those defined by the applicant for of non-inferiority (6), the older one from 2008 (4 RCTs) showed better serological cure with benzathine penicillin (OR 1.75, 1.03-2.97).(7) The applicant considered the evidence to point towards prioritizing doxycycline over azithromycin for *C. trachomatis* urethritis, and shows a questionable benefit of benzathine penicillin over azithromycin for the treatment of syphilis.

Guidelines (from the application)	McMaster Group: The highest ranked guideline specific for urethritis which was developed by the European Association of Urology(8), recommends ceftriaxone or cefixime 800mg plus azithromycin for empiric treatment given the increase of fluoroquinolone resistance in gonococcal infections. 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 alternative regimens.(9) Azithromycin is a second line agent and is recommended if the patient has infection with *Mycoplasma genitalium*. It should not be used routinely because of concern of macrolide resistance with *M. genitalium*. For persistent or recurrent non-gonococcal urethritis, if doxycycline was used as the first line treatment, then azithromycin and metronidazole can be used if *Trichomonas vaginalis* is prevalent in the local population. If azithromycin was used as first line, the recommended regimen is then moxifloxacin and metronidazole. The UK guidelines recommend doxycycline as the most effective treatment options, or a single dose of azithromycin with ofloxacin as an alternative.(10) CDC guidelines 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 penicillin G or procaine penicillin as the next best alternative for both adults and children as first line treatment. Alternative options if a patient is allergic to penicillin include doxycycline. The use of ceftriaxone or azithromycin and erythromycin are discouraged unless there are no other options. Aqueous benzyl penicillin is recommended for congenital syphilis, with procaine penicillin as an alternative. The UK guidelines from 2015 also recommend benzathine penicillin G as first-line therapy, and azithromycin or doxycycline as a second-line alternative with the caution of increasing resistance to this agent.(13) Other options listed as alternative regimens include ceftriaxone and amoxicillin, and erythromycin only if no other options are available. For neurosyphilis, procaine penicillin G with concomitant probenecid is recommended as first choice. For congenital syphilis, again, benzyl penicillin and procaine penicillin are options. More or less identical recommendations were made in the 2015 CDC guideline.(11) However, the CDC recommends aqueous crystalline penicillin G as first line for neurosyphllis instead of procaine penicillin G and probenecid, which are recommended as an alternative agent.
Rationale for antibiotic selection (from the application)	McMaster Group: For gonococcal urethritis, ceftriaxone as an IV/IM option and cefixime as an oral option were proposed. Doxycycline was recommended as the core antibiotic for the treatment of chlamydial/non-gonococcal urethritis, with or in favour of azithromycin as suggested by the majority of guidelines. Furthermore, based on the evidence from systematic reviews that the efficacy of azithromycin is decreasing in more recent years, and the black boxed warning by FDA in terms of safety for azithromycin, azithromycin should only be used if doxycycline failed or is contraindicated, or if there are major concerns with adherence to a multiple-day regimen of doxycycline. For syphilis, penicillin G in various forms were proposed, depending on the form of syphilis to be treated. Of the antibiotics listed in the guidelines, fluoroquinolones, which in most instances are only listed as second or third line antibiotics, were not proposed for inclusion, given that multiple preferred options are already listed. Tetracycline and lymecycline were also not proposed due to redundancy with doxycycline, which is already listed for several other infectious syndromes. Erythromycin was not proposed due to more adverse events than azithromycin, and the recommendation to avoid it as first or second line for syphilis.

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	Other than congenital syphilis, these sexually-transmitted infections are, with a few exceptions, limited to the adult population, thus, the identified SR and CPGs 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: *1. 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. *2. 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. *3. 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. *4. 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. *5. 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* • benzathine penicillin G 2.4 million units once intramuscularly over no treatment • benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10–14 days intramuscularly.

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	When benzathine or procaine penicillin cannot be used: • doxycycline 100 mg twice daily orally for 14 days; OR • ceftriaxone 1 g intramuscularly 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* • benzathine penicillin G 2.4 million units once intramuscularly over no treatment. • benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once daily for 10 days When benzathine or procaine penicillin cannot be used: (with caution) • erythromycin 500 mg orally four times daily for 14 days; OR • ceftriaxone 1 g intramuscularly 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* • benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment. • benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units 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* • benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment • benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units intramuscularly once a day for 20 days When benzathine or procaine penicillin cannot be used: (with caution) • erythromycin 500 mg orally four times daily for 30 days. *Congenital syphilis in infants* • benzyl penicillin 100 000–150 000 U/kg/day intravenously for 10–15 days • procaine penicillin 50 000 U/kg/day single dose intramuscularly for 10–15 days
WHO Guidelines: *Chlamydia trachomatis*	The 2016 WHO guidelines for the treatment of *Chlamydia trachomatis (15)* make the following recommendations: *1. 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. *2. 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. *3. 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.

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4. Lymphogranuloma venereum
In order of preference:

- doxycycline 100 mg orally twice daily for 21 days
- azithromycin 1 g orally, weekly for 3 weeks.

5. Chlamydial ophthalmia neonatorum
In order of preference:

- azithromycin 20 mg/kg/day orally, one dose daily for 3 days
- erythromycin 50 mg/kg/day orally, in four divided doses daily for 14 days.

6. 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:
(eg. additional evidence, dose/duration, costs etc)

The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for allergy were not considered. The Committee considered the various antibiotics proposed in the applications and aligned recommendations to WHO STI guidelines for combination therapy (gonorrhoeae) and included additional second choice medicines (gentamicin and spectinomycin).

Recommended first and second choice antibiotics are reported below.

EML listings: STIs
Antibiotics proposed for both EML and EMLc unless specified

FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc

FOR 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 (EML)
	Procaine benzylpenicillin (EMLc)	
	Benzylpenicillin	
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 penicillin (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 (COPD)

Exacerbations of chronic obstructive pulmonary disease (COPD)	
Applicant(s):	McMaster Group
Introduction: Description of the condition / infecting organisms / public health need?	Exacerbations of chronic obstructive pulmonary disease are an important health care burden. Although treatment can involve bronchodilators and anti-inflammatory agents including steroids, use of antimicrobials is frequent on the basis that a bacterial infection is suspected to act as a trigger to the episode. Of note, antibiotics are only indicated in 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 RCTs, 2068 participants).(1) There was not a significant benefit of using antibiotics over not using antibiotics for outpatients when restricted to available antibiotics (RR 0.80, 95%CI 0.63 to 1.01) but there was evidence for inpatients (RR 0.77, 95%CI 0.65 to 0.91). A older and lower quality systematic review, in contrast, found a small clinical benefit with antibiotic treatment without giving further specification on the population who benefited (9 RCTs, 1101 patients).(2) Similarly, a systematic review from 2008 (10 RCTs, 959 patients) 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 in 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 however were not designed to compare antibiotics. Two reviews were identified that compared different antibiotic agents. One review compared first line to second line antibiotics (12 RCTs, 2,261 participants) and reported that first line antibiotics (amoxicillin, ampicillin, pivampicillin, trimethoprim+sulfamethoxazole, and doxycycline) were associated with lower treatment success compared to second line agents (amoxicillin+clavulanic acid, macrolides, second-generation or third-generation cephalosporins, and quinolones), OR 0.51, 95%CI 0.34 to 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 first line antibiotics. The review by Korbila et al. (5 RCTs, 287 patients), found no differences in treatment success, adverse events, or mortality between patients treated with penicillins and those treated with trimethoprim+sulfamethoxazole, but did not meet the applicant's criteria for non-inferiority.(5) In terms of duration of treatment, one systematic review including 21 RCTs and 10,698 patients compared the outcome for short duration (up to 5 days) to longer durations.(6) The authors did not find any difference in efficacy with reasonably small confidence intervals (RR 0.99, 95% CI 0.90-1.08 for clinical cure at the 4-week mark). This was confirmed by a systematic review in the same year with fewer studies included.(7) In summary, the randomized controlled evidence was insufficient for the applicants to recommend one antibiotic or class of antibiotics over another, therefore, guidelines informed the choices of antibiotics for the essential medicines list. 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, moxifloxacin, were potential antibiotics, depending on local bacterial resistance patterns. For hospitalized patients, amoxicillin+clavulanic acid, respiratory fluoroquinolones (levofloxacin and moxifloxacin), and combination therapy if Pseudomonas and other gram negatives were suspected. The NICE guidelines recommend antibiotics only if there is purulent sputum or clinical or radiographic evidence of pneumonia in which case an aminopenicillin, macrolide, or a tetracycline could be used, taking into account local resistant patterns.(9)

The Canadian guideline distinguishes 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 trimethoprim+sulfamethoxazole are recommended. In complicated bronchitis (with risk factors), fluoroquinolones and betalactam/betalactamase inhibitors are recommended. For chronic suppurative bronchitis, targeted treatment of the identified pathogen is recommended.

The FDA published a boxed warning against the use of fluoroquinolones for this indication related to several side effects associated with antibiotics of this class (11). The main concerns were related to disabling and potentially permanent side effects of the tendon, muscles, joints, and include also peripheral neuropathy and central nervous system effects, reported also in otherwise healthy patients. The FDA continues to recommend the use of fluoroquinolones in life threatening infections where the potential benefit outweighs the potential risk.

Rationale for antibiotic selection
(from the application)

Based on the guidelines, amoxicillin +/- clavulanic acid and a cephalosporin (cefuroxime or cefalexin) were proposed as core antibiotics as these provide appropriate coverage. Clarithromycin and doxycycline are alternatives if betalactams or cephalosporins cannot be used. Azithromycin was not proposed as an alternative to clarithromycin due to safety concerns. Dirithromycin and roxithromycin were not listed as there is no benefit compared to clarithromycin, which is also recommended for other syndromes. Trimethoprim+sulfamethoxazole was not proposed as it was only listed in one of the guidelines and is not frequently used for this indication. Due to the side effect profile of fluoroquinolones and the emergence of resistance, levofloxacin should only be used if no other better options of the antibiotics listed here are available. Moxifloxacin was not proposed as it is not considered superior to levofloxacin, but levofloxacin is listed for several other indications.
Given that COPD is a disease of the adult patient population, it was not surprising that no systematic reviews data or guidelines were found to guide management in the paediatric population. Therefore, no dosing recommendation for paediatric patients were made.

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

The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. 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. The first choice antibiotics are those generally recommended based on available evidence and are usually narrow spectrum agents.

EML Listings: exacerbations of COPD
Antibiotics proposed for both EML and EMLc unless specified

FOR 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	
	Amoxicillin + clavulanic acid	Cefalexin
		Doxycycline

Committee Recommendations:

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

The Expert Committee endorsed the inclusion on the EML of amoxicillin and amoxicillin +

	clavulanic acid as first choice therapy and cefalexin and doxycycline as second choice therapy for use in suspected bacterial exacerbations of COPD.

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Bone and joint infections

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. The latter are increasing in incidence due the ever increasing number of join replacements. Because treatment is rarely empiric and targeted treatment based on microbiology is highly emphasized for this type of infections, the applicant considered antibiotics for empiric as well as targeted treatment.
Summary of evidence: (from the application)	One Cochrane review compared antibiotics for treating chronic osteomyelitis in adults.(1) There were only 8 small RCTs totalling 282 participants, which provided very limited information because of lack of power such that no significant differences could be noted 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) to various betalactams (imipenem+cilastatin, ampicillin+sulbactam, amoxicillin+clavulanic acid, cefazoline or ceftazidime, broad spectrum cephalosporins or nafcillin-aminoglycoside) for osteomyelitis (7 RCTs, 411 participants).(2) There was no difference in treatment success for osteomyelitis between fluoroquinolones and beta-lactams (194 patients, OR 0.99, 95% CI 0.51-1.91), again, with wide confidence intervals not meeting non-inferiority criteria. Given the small size of the studies and 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 essential medicines list.
Guidelines (from the application)	The IDSA guidelines for prosthetic joint infections provide recommendations for various situations of prosthetic joint infection.(3) Where the prosthetic joint is retained after debridement, they recommend pathogen specific therapy in combination with rifampicin, including nafcillin, cefazolin, or ceftriaxone for methicillin susceptible Staphylococci, vancomycin for methicillin resistant Staphylococci, penicillin or ampicillin for Enterococcus spp that are penicillin susceptible, vancomycin for Enterococcus that are penicillin resistant, cefepime or meropenem for *P. aeruginosa*, cefepime or ertapenem for Enterobacter sp, an intravenous beta-lactam based on susceptibility or ciprofloxacin for Enterobacteriaceae, penicillin or ceftriaxone for beta-hemolytic streptococci, and penicillin or ceftriaxone for Propionibacterium acnes. An oral antibiotic (ciprofloxacin or levofloxacin), or trimethoprim+sulfamethoxazole, minocycline, doxycycline**,** or oral first-generation cephalosporins (eg, cefalexin) or antistaphylococcal penicillins along with rifampicin is recommended for infections from methicilin-susceptible *S. aureus*. Cephalexin, dicloxacillin, trimethoprim+sulfamethoxazole, or minocycline are recommended as choices for chronic suppressive therapy following an initial treatment course if required. When the treatment is a 1-stage approach, a similar approach, i.e. pathogen specific therapy with rifampicin followed by longer-term oral antibiotics with rifampicin is recommended for patients with *S. aureus* infections. The same antibiotics are recommended, as they are for chronic suppression. The IDSA guidelines for vertebral osteomyelitis suggested a combination of vancomycin and a third- or fourth-generation cephalosporin for empiric use if required, but the general approach is to determine the pathogen and target the organism.(4) First line antibiotics for pathogens are the same as those for prosthetic joint infections with the addition of ciprofloxacin for Salmonella species.

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Rationale for antibiotic selection (from the application)	Based on the epidemiology of pathogens typically encountered in this type of infections, the applicant proposed the most appropriate antibiotics for possible empiric and targeted treatment. Empiric treatment should be avoided unless patients need immediate antibiotic treatment, or if it is impossible to obtain a sample for microbiology for other reasons. Empiric antibiotic choice should be based on the pathogens suspected to be most likely involved. As treatment heavily depends on the identified pathogen, no distinction between core and targeted antibiotics was made, so all antibiotics were proposed in a single group (i.e. core) for this syndrome. Of the antibiotics proposed in the guidelines, cefepime was not proposed for inclusion on the EML due to safety concerns (refer to the febrile neutropenia summary) in a setting where an alternative agent is available (meropenem), however, it 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, as doxycycline was proposed for this and several other syndromes. Dicloxacillin, rather than nafcillin, is proposed as an anti-staphylococcal penicillin, as the former is listed for several other syndrome. 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, thus, no recommendation for dosage in children was proposed.
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. As a result, the following antibiotics were excluded: – ampicillin, penicillin G, levofloxacin, ciprofloxacin, trimethoprim-sulfamethoxazole, and doxycycline, since these antibiotics are mostly used as targeted (documented) 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 (which has a square box), and considered that any IV anti-staphylococcal penicillin would be appropriate. For oral administration, cloxacillin, dicloxacillin and flucloxacillin are preferred due to better bioavailability. Recommended first and second 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: bone and joint infections Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc	

	FIRST CHOICE	SECOND CHOICE
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 empiric treatment of bone and joint infections and ceftriaxone,cefotaxime,

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	cefazolin, clindamycin and amoxicillin + clavulanic acid as second choice therapy in bone and joint infections. All inclusions apply to both the EML and EMLc.

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Febrile neutropenia

Febrile neutropenia	
Applicant(s):	McMaster group
Introduction: Description of the condition / infecting organisms / public health need?	Febrile neutropenia is a severe infectious syndrome needing empiric treatment in immunocompromised patients.
Summary of evidence: (from the application)	One systematic review compared various beta-lactam regimens for empiric therapy for febrile neutropenia (33 RCTs, 4,242 participants) and found that cefepime was associated with higher all-cause mortality at 30 days than other beta-lactams (RR 1.44, 95% CI 1.06 to 1.94).(1) Adverse events were significantly more frequent with carbapenems, specifically pseudomembranous colitis (RR 1.94, 95% CI 1.24–3.04, 2025 participants) although they were associated with fewer treatment modifications, which is considered a negative outcome. Piperacillin-tazobactam had a lower rate of adverse events than comparators (RR 0.25, 95%CI 0.12-0.53). A more recent Cochrane review (44 RCTs, 3,471 participants) also reported a significantly higher mortality with cefepime compared to other beta-lactams (RR 1.39, 95% CI 1.04 to 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, inferiority of cefepime was refuted by a meta-analysis conducted by the FDA (88 trials, 9,467 cefepime patients and 8,288 comparator patients) which found no difference in death and confirmed their findings by doing a patient-level meta-analysis.(3) However, this meta-analysis was not specific to studies in febrile neutropenia. Studies in febrile neutropenia contributed 24 of the studies, as the majority of studies included were conducted in other populations: pneumonia trials (n=26), trials in intra-abdominal infections (n=7), urinary tract infection (n=7), and others (n=24). Another Cochrane review, the highest ranked in the application amongst the systematic reviews comparing different regimens, compared beta-lactam versus beta-lactam plus aminoglycoside combination therapy in patients with febrile neutropenia (71 RCTs).(4) The authors found similar results for mortality for trials comparing the same beta-lactam (RR 0.74, 95% CI 0.53 to 1.06) and for trials comparing a broad-spectrum beta-lactam compared with a narrower-spectrum beta-lactam combined with an aminoglycoside (RR 0.91, 95% CI 0.77 to 1.09). Infection related mortality was significantly lower with monotherapy (RR 0.80, 95% CI 0.64 to 0.99), and there were significantly more adverse events with combination treatment with a number needed to harm of 4 (95% CI 4-6). Similar findings were reported in a Cochrane review from 2003 and a non-Cochrane review from 2002.(5, 6) In a 2014 Cochrane review, empiric antibiotics for gram-positive bacteria for febrile neutropenia was assessed (13 RCTs, 2,392 patients).(7) No significant difference in mortality was noted when using a glycopeptide as part of the initial regimen (RR of 0.82, 95% CI 0.56 to 1.20) as well as no difference on treatment failure was noted (RR 1.0, 95% CI 0.79-1.27). In contrast, an older and lower ranked systematic review found higher success rates by adding glycopeptides (OR 1.63, 95% CI 1.17-2.28).(8) No differences for mortality outcomes were found, however, adverse events were more frequently encountered when adding glycopeptides (OR 4.98, 95% CI 2.91-8.55). A systematic review of fluoroquinolones in low risk children with fever and neutropenia (6 RCTs and 4 cohort studies) reported no difference in treatment failure as compared to comparators (RR 1.02, 95% CI 0.72 to 1.45).(9) Inferences here were limited given that the definition for treatment failure included antibiotic modification and that study quality was not assessed. Another review compared ciprofloxacin with a beta-lactam to an aminoglycoside with 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 to 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 intravenous antibiotics in patients with febrile neutropenia (excluding leukemia) who were haemodynamically stable, without organ failure, and did not have pneumonia, central line or severe soft-tissue infections (treatment failure RR 0.96, 95% CI 0.86-1.06), but exceeded the applicant's definition of non-inferiority, as did the comparison of mortality rates (RR 0.95, 95% CI 0.54-1.68).(11) In summary, there is no role for a combination with aminoglycoside in empiric treatment of febrile neutropenia as there is no clinically relevant benefit and only an increase in adverse events as compared to beta-lactam monotherapy. The same is true for routine use of glycopeptides (e.g. vancomycin) based on the highest ranked SR: no benefit in clinical cure but a higher rate of adverse events. Ciprofloxacin in combination with a beta-lactam was found to marginally superior to beta-lactam/aminoglycoside combinations. However, this is based on evidence published before 2005 when fluoroquinolone resistance had less significance than nowadays. While this supports the notion that aminoglycosides should not be used routinely in this patient population, no conclusions can be made on the potential benefit of fluoroquinolones given today's epidemiology of fluoroquinolone resistance. Overall, no single agent or regimen was found to be clearly superior to other standard regimens, thus, clinical guidelines guided proposals for inclusion into the essential medicine list. The exception was cefepime,e that has been shown to be associated with a higher risk of death in several systematic reviews and is as such not considered a candidate to the core or targeted list.
Guidelines **(from the application)**	The 2010 IDSA guidelines recommend that monotherapy with an anti-pseudomonal 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 with beta-lactam allergies include also aztreonam. Empiric treatment for persisisting fevers after 4 days of broad spectrum antibiotics includes empiric antifungals, e.g. echinocandines, voriconazole, or amphotericin B (beyond the scope of this review). Ciprofloxacin plus amoxicillin+clavulanic acid in combination is recommended for oral empirical treatment in low risk patients. The NICE guideline recommends monotherapy with piperacillin+tazobactam.(13) The use of empiric 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 for children to use monotherapy with an antipseudomonal beta-lactam or a carbapenem as empiric therapy in high-risk paediatric patient.(14) A second gram-negative agent or glycopeptide should be added for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens.

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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 adults as well as for children, was proposed as a core antibiotic. Cefepime was not proposed for inclusion in the EML as it was felt to be redundant with the antibiotics already listed above, and the potential concern about inferiority in terms of mortality. However, it has a potential role as a carbapenem-sparing agent for other indications and is as such proposed for inclusion on the preserved list as a niche antibiotic. Colistin, aztreonam, daptomycin, linezolid, and tigecycline that are all proposed as antibiotics for the preserved list as alternative agents for febrile neutropenia and other indication if none of the here listed antibiotics are deemed appropriate due to resistance or other concerns. Ceftazidime was not proposed due to redundancy with 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 and not imipenem+cilastatin was proposed due to redundancy and the fact that meropenem is recommended for other syndromes. Meropenem, aminoglycosides, and vancomycin are to be used only if needed in addition to or instead of the first line regimen, piperacillin+tazobactam, 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: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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. As a result, gentamicin was excluded. Amikacin was preferred to gentamicin because it is usually more frequently active on Enterobacteriaceae. Recommended first and second choice antibiotics are reported below. The first choice antibiotics are those generally recommended based on available evidence and are usually narrow spectrum agents.
Listings: febrile neutropenia Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc	The Expert Committee made recommendations in line with Talcott criteria for risk classification (15).

	FIRST CHOICE	SECOND CHOICE
ENDORSEMENT	Low risk: Amoxicillin + clavulanic acid	
	Low Risk: Ciprofloxacin	
		High Risk: Vancomycin IV
ADDITION	High Risk: Piperacillin + tazobactam	High risk: Meropenem
	High Risk: Amikacin	

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 Expert 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 Expert 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

Severe acute malnutrition (SAM)	
Applicant(s):	WHO Department of Maternal, Newborn, Child and Adolescent Health
Introduction: Description of the condition / infecting organisms / public health need?	Severe acute malnutrition (SAM) affects nearly 20 million children under 5 years, causing up to 1 million deaths each year by increasing susceptibility to death from severe infection (1). The most susceptible age for malnutrition is 6 to 18 months, but it is increasingly recognised that SAM may occur in infants aged younger than 6 months (2). SAM is classified according to the absence of presence of medical complications (3): i) 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 to indicate the absence of severe metabolic disturbance. Patients are deemed to be most appropriately managed as outpatients, with ready-to-use therapeutic foods; ii) 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 an outpatient 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 systematic search for systematic reviews, meta-analyses, multicentre studies and randomized controlled trials was conducted, and 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). The current evidence supports administration of amoxicillin 80 mg/kg/day in two divided doses for 7 days to children with SAM in the community setting. For complicated SAM, the evidence supports the continued recommendation of empiric 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 treatment of complicated SAM, many of which pre-date recent trials. The 2013 WHO guidelines for treatment of SAM make the following recommendations regarding antibiotic treatment of SAM: • children with uncomplicated severe acute malnutrition, not requiring to be admitted and who are managed as outpatients, should be given a course of oral antibiotic such as amoxicillin (conditional recommendation, low-quality evidence); • children who are undernourished but who do not have severe acute malnutrition should not routinely receive antibiotics unless they show signs of clinical infection (strong recommendation, low-quality evidence). • children admitted with severe acute malnutrition 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 severe acute malnutrition and with no apparent signs of infection and no complications should be given an oral antibiotic.
Rationale for antibiotic selection	Alignment with WHO guidelines.

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(from the application)	
Committee considerations: (eg. additional evidence, dose/duration, costs etc)	The main focus has been on empiric treatment choices for common community-acquired infections that are broadly applicable in the majority of countries. Generally, alternative options for 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 this indication in alignment with the WHO guidelines for inclusion on the EMLc. Second choice therapies were neither proposed nor recommended. Recommended first choice antibiotics for uncomplicated and complicated SAM are reported below.
EML listings: SAM Antibiotics proposed for both EML and EMLc unless specified FOR ENDORSEMENT indicates those antibiotics currently included on EML/EMLc FOR ADDITION indicates new antibiotics not currently on EML / EMLc	

	FIRST CHOICE - EMLc	SECOND CHOICE
ENDORSEMENT	**Uncomplicated SAM** amoxicillin	-
	Complicated SAM benzylpenicillin ampicillin gentamicin amoxicillin	-

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 benzylpenicillin or ampicillin and gentamicin followed by amoxicillin as first choice therapy in use in complicated severe acute malnutrition.

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UNEDITED VERSION

Preserved antibiotic list – EML and EMLc

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 syndromes and largely on empiric use, that is, use for suspected infection in the absence of (or pending) microbiologic evidence for a 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 was comprised of antibiotics that are positioned here for several different reasons.

One of the most important reasons is *preservation* of certain antibiotics when there are currently alternatives that often are safer. Antibiotics proposed for this reason are meant to be preserved for when they are really needed given a patient's specific circumstances (e.g. intolerance or resistance to core and targeted antibiotics), or for future use when there are very high resistance rates to the proposed core and targeted antibiotics. As such they are considered last resort antibiotics. One such antibiotic is colistin which is a polymyxin antibiotic that can be used for multi-resistant organisms, such as extremely multi-resistant *Pseudomonas aeruginosa* or Acinetobacter species. However, the drug carries a risk of nephrotoxicity and should be used judiciously, that is not if other options in less resistant strains are available. Tigecycline is similar in that it has a relatively broad spectrum of activity, including both gram positive and gram negative pathogens. However, the FDA issued a black box warning in 2010 due to concern about an increased risk of death. For this reason, the applicant considered this antibiotic should be considered a last resort antibiotic to be used only when an alternative agent is not suitable.

Other proposed antibiotics were considered "niche" antibiotics in that they should have a narrower range of uses predicted on the pathogen isolated. Linezolid, for example, has expanded gram positive activity being active against gram positive organisms such as vancomycin-resistant enterococcus (VRE) and Methicillin-resistant *Staphylococcus aureus* (MRSA). Resistance to this antibiotic can develop but remains low, which is why it should be used selectively. Daptomycin also has excellent gram positive activity and should be preserved given that resistance is currently low. Rifampin, used for non-tuberculous infection as an adjunct therapy for rifampin-susceptible staphylococci 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 a day dosing in the outpatient setting, in particular for coverage of pathogens with a certain degree of resistance against core and targeted antibiotics, e.g. extended-spectrum beta-lactamase producing enterobacteriaceae. In addition to niche indications, carbapenem shouldbe preserved to avoid development of more widespread resistance to carbapenems.

Other antibiotics, such as cefepime, aztreonam, and moxifloxacin were also on the proposed list of preserved antibiotics in order to prevent further resistance. They generally have a reasonable safety profile and have good activity (e.g cefepime as a fourth generation cephalosporin has excellent gram negative activity, aztreonam has good gram negative activity especially covering *Pseudomonas aeruginosa*, and moxifloxacin has activity expected of a respiratory fluoroquinolone). However, other antimicrobials exist with similar coverage. These antibiotics are placed on this list to preserve them should existing agents become ineffective.

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The proposals from the application for **Conserved Antibiotics List** McMaster group are described in the table below:

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 Antibiotics RESERVE Group

The Expert Committee considered the various antibiotics as proposed in the McMaster application for conservation, and adapted it to create the EML Antibiotics RESERVE Group by 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 in order to improve targeted access according to available recommendations and reduce the risk of selection of resistance to these last-resort antibiotics.

The Expert Committee excluded moxifloxacin from this group, as fluoroquinolones are already included in the Stewardship WATCH group. Similarly, ertapenem was excluded as carbapenems are included in the WATCH group (as 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. The Expert Committee agreed that inclusion of aztreonam, tigecycline and daptomycin on the RESERVE group was appropriate.

The Expert Committee listing of the Antibiotics RESERVE Group ("LAST RESORT") is described in the Table below:

RESERVE group ('last-resort') 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

The Reserve group Includes antibiotics that should be treated as 'last-resort' options that should be accessible when needed, but whose use should be tailored to highly specific patients and settings, when other 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 high-intensity national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

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6.2.2 Other antibacterials

Azithromycin – 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:	Dr Oriol Mitjà, Laia Bertran – The Barcelona Institute for Global Health
WHO Technical Department:	Department of Control of Neglected Tropical Diseases
EML / EMLc	EML and EMLc
Section:	6.2.2 Other antibacterials
Dose form(s) & strengths(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, eg. resubmission, previous EC consideration)	Azithromycin is currently available on the EML and EMLc only for single-dose treatment of genital *Chalmydia trachomatis* and of trachoma.
Public health relevance: (burden of disease)	Yaws is an infectious, neglected tropical disease (NTD) caused by the *Treponema pallidum pertunue* bacterium. It produces 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 – Papua New Guinea, Solomon Islands and Ghana (3). In 2012, WHO revised its global eradication policy for yaws and developed the "Morges Strategy" with the goal of eradicating yaws by 2020 (4). New "mass drug administration" policies were recommended which involve total community treatment and total targeted treatment with oral azithromycin or injected benzathine penicillin 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 demonstrated a rapid drop in prevalence (5).
Summary of evidence: benefits (from the application)	Single-dose azithromycin has been demonstrated to be non-inferior to single dose intramuscular benzathine penicillin in the treatment of yaws in two recent open-label randomized trials (6, 7). A trial in 250 children in Papua New Guinea showed a single oral dose of azithromycin 30 mg/kg (up to 2 g) to produce clinical and serological cure of yaws in 96.4% of cases, compared to 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 meet the pre-specified criteria for non-inferiority (6). A similar trial in Ghana involving 353 children found similar results. Clinical cure of yaws at 3 weeks was demonstrated in 98.2% and 96.6% of azithromycin and benzathine penicillin treated patients, respectively (RD -1.3, 95% CI -4.7 to 2.0). Serological cure at 6 months was achieved in 57.5% and 49.1% of azithromycin and benzathine penicillin treated patients, respectively (RD -8.3, 95% CI:-19.1 to 2.4). The pre-specified 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 the studied population received mass treatment with single-dose azithromycin and were monitored for one year. The prevalence of active yaws decreased from 2.4% to 0.3% (difference -2.1%; 95%CI, 1.9 to 2.4), and the prevalence of latent yaws with high-titre seroreactivity in children decreased from 18.3% to 6.5% (difference 11.8%, 95% CI 8.9 to 14.7). The effect was most notable in children aged 1 to 5 years, with high-titre seroreactivity in this subgroup close to zero one year after treatment. A study by Aziz Abdulai et al (9) conducted in a target population of 15,310 people in Ghana also found decreased prevalence of polymerase chain reaction (PCR)-positive active yaws from 3.1% to 0% (difference -3.1%, 95% CI 2.1 to 4.4) and the rate of latent yaws from 10.7% to 2.1% (difference -8.7%, 95% CI 6.6 to 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 have assessed the impact on yaws of azithromycin mass drug administration for trachoma (10, 11). Each found benefit with regard to ongoing transmission of yaws or post-treatment prevalence of yaws.
Summary of evidence: harms (from the application)	No severe adverse events attributable to the study drug were reported by means of passive surveillance during a large longitudinal study of 13,490 participants administered single-dose azithromycin 30 mg/kg as MDA for yaws. Active surveillance of 316 participants from 60 households yielded 54 participants (17.1%) who reported adverse events (all mild), including 30 (9.5%) with nausea or abdominal pain, 25 (7.9%) with diarrhea, and 15 (4.7%) with vomiting (8).
Additional evidence: (not in the application)	Since submission of the application, the study by Kwakye-Maclean et al, comparing single dose oral azithromycin and IM benzathine penicillin in a randomized non-inferiority trial in Ghana has been published in PLoS NTD (7).
WHO Guidelines:	Azithromycin given orally is preferred to benzathine penicillin. 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 penicillin 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 azithromycin, those who 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 over 10 years.
Costs / cost-effectiveness:	The application presented a comparison of costs for benzathine penicillin and azithromycin for yaws based on WHO recommended doses. Taking into account non-drug costs associated with administration of benzathine penicillin, azithromycin was found to be the cheaper option for the 6-9 and 10-15 years age groups. 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 drug acquisition and administration of low-cost generic azithromycin formulations are highly competitive. This suggests scope for negotiation of lower prices at country procurement level.
Availability:	Azithromycin is widely available, with multiple 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 to 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 – 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 (MDR-TB).
Applicant:	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) & strengths(s):	Capsule: 50mg, 100mg
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 M/XDR-TB (1, 2).
Public health relevance: (burden of disease)	It is estimated that there are 580,000 new rifampicin-resistant and multidrug-resistant TB (RR-/MDR-TB) cases world-wide 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. XDR-TB) (3). In 2015, countries reported that about 125,000 MDR/RR-TB patients and over 7,000 XDR-TB patients started treatment. Outcome reporting data has shown that approximately half 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.

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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. <u>Clofazimine in adults (Annex 2a):</u> One small RCT of 105 patients (5) assessed treatment success compared to treatment failure or death in non-XDR, MDR-TB patients and concluded a not statistically significant absolute benefit of 200 more treatment successes per 1000 patients treated with clofazimine (95% 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 6 studies in MDR/XDR patients (1 RCT, 5 cohort) concluded a not 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 concluded 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 submission 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 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 DR-TB (8). Treatment success ranged from 16.5% (95% CI 2.7-38-7) to 87.8% (95% CI 76.8%, 95.6%) between countries 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 submission noted that the success rates reported in Gopal et al (7) and Dey et al (8) are higher than usually reported in M/XDR-TB patients and that inclusion of heterogeneous treatment regimens, and biases and residual confounding associated with observational studies might account, in part, for these results. <u>Clofazimine in children (Annex 2b):</u> Individual patient data meta-analysis of 9 observational studies (623 patients) was conducted by Harausz et al (unpublished, with summary in (6)). It assessed treatment success versus failure/relapse/death in MDR-TB patients and concluded a non-statistically significant benefit of clofazimine treatment in confirmed MDR-TB cases (adjusted odds ratio (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. <u>Clofazimine in shorter MDR-TB cases (Annex 2c):</u> A meta-analysis of 37 observational studies (using an indirect comparison of two aggregate data meta-analyses of 6 studies of shorter duration regimens [preliminary data from 3 series and data from three published studies] and 31 studies of conventional MDR regimens assessed 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 standardised 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 submission suggested that the adverse event profile for clofazimine is known from its use in the treatment of leprosy. Annex 2a summarises 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 5 comparative observational studies and 12.8% assessed in 6 uncontrolled observational studies. Event rates were 3.3% in non-tuberculosis mycobacterium (NTM) assessed in 4 comparative observational studies (6). The quality of all of these 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% to 46.1%), while the proportion of patients with ADRs requiring discontinuation of clofazimine was 0.1% (95% CI: 0.0% to 0.6%) (9). There are few data on adverse event rates in children. The submission reported that 75%-100% of patients develop orange-red skin pigmentation which is usually reversible months to years after treatment cessation. 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 anti-fungals) may have additive adverse effects. The submission 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 M/XDR-TB treatment included clofazimine in the 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 M/XDR-TB (See Table 1 of the submission) (1).
Costs / cost-effectiveness:	The submission provided several indicative prices at June 2016 based on the use of clofazimine to treat leprosy, e.g. US$109.48 for 100 caps of 100mg; and US$0.547-0.713 per 50mg capsule.
Availability:	While clofazimine is registered by a number of regulatory agencies (including US FDA, EMA, Australian TGA, 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 the updated WHO guidelines for the management of MDR-TB 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 the indications for clofazamine 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 – 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:	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) & strengths(s):	Tablet: 50mg
Core / Complementary:	Complementary
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 for the treatment of patients with multidrug-resistant tuberculosis (MDR-TB) to the WHO EML for adults (2). In 2016, following a review of paediatric data, WHO guidance was extended 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) disease (3, 4).
Public health relevance: (burden of disease)	Of an estimated 10.4 million incident TB cases globally in 2015, 1 million occurred in children. There are estimated to be 580,000 new MDR/RR-TB cases world-wide annually and about 250,000 MDR/RR-TB patients die. Many MDR/RR-TB cases, including children, go undetected and are not placed on 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 4 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 to 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 (242-07-204), an open observational trial (242-07-208) and an observational study (242-10-116). Confidential raw data from pre-clinical studies in children (trials 242-12-232 and 242-12-233) were provided by Otsuka. The quality of data available was assessed as very low. Evidence of benefit from RCT 204 was based on surrogate outcomes: sputum culture conversion (SCC) to negative at 2 months, and time to culture conversion at 2 months. Observational study 208 reported sustained SCC at 24 months 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 (RR 1.60; 95% CI 1.18, 2.18 and 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)	There were small numbers of serious adverse events reported in trial 204, 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 would be generalizable to under-18 year olds (QT prolongation over 2 months, trial 204, 9.9% vs 8.8%; RR 2.65; 95% CI 1.08, 5.99). QT prolongation by more than 60 msec was reported in 7.5% of delamanid-treated patients compared to no patients receiving an optimized background regimen (OR 12.81; 95% CI 1.65, 99.7). Acquired resistance to delamanid was not estimable in studies 204 and 208.
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 5 conditions (3, 4): (i) Delamanid may not be warranted if an effective regimen can be composed with other second line medicines, however, may be justified in patients at high risk of poor outcomes. Due to concerns about QTc prolongation, children with a QTcF > 500 ms should not receive delamanid. (ii) 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. (iii) Supervised treatment should be adapted to twice daily administration of delamanid. (iv) Active TB drug safety monitoring is required particularly for QTc interval prolongation and cardiac dysrhythmias, and monitoring electrolyte disturbances (especially potassium). (v) Patient informed consent is obtained from the parent or guardian. The health authority may also require that the child/adolescent would also assent to receive delamanid.
WHO Guidelines:	Table 1 of the application summarises 2016 WHO policy recommendations for the treatment of rifampicin-resistant and multi-drug resistant 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 USD1700 for a six-month treatment in adults was announced by the Otsuka Pharmaceutical Company. All countries eligible for financing through the Global Fund to Fight AIDS, TB and Malaria and which follow WHO guidelines for MDR-TB management in quality-assured programmes could procure delamanid through GDF at this price. Prices in high income countries are much higher, e.g. GBP17,500 for a 24-week course in the United Kingdom and about USD33,000 for a six-month course of 100 mg twice daily in Germany.
Availability:	Marketing authorization in Europe, Japan, Hong Long SAR, China 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 to 17 years. The Expert 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 was recommended for the listing of delamanid for adults in 2015, the Expert Committee recommended that delamanid for the treatment of children should only be introduced in settings where close monitoring of patients and active pharmacovigilance can be ensured.

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UNEDITED VERSION

Gatifloxacin – addition – 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 (MDR-TB).
Applicant:	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) & strengths(s):	Tablet: 200mg; 400mg
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 MDR-TB regimens and longer regimens for M/XDR-TB (1, 2). Currently, the EML and EMLc includes 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 there are 580,000 patients who develop rifampicin-resistant or MDR-TB globally each year and who would need second-line TB treatment regimens to increase their likelihood of a successful treatment outcome (3). In many low resource settings, there are often not enough medications available to compose a suitable regimen for drug resistant TB and global 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.

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Summary of evidence: benefits (from the application)	A review of the available evidence for the effectiveness and harms of gatifloxacin was undertaken for the 2016 revision of the WHO treatment guidelines for MDR-TB (1). The GRADE table summarising the evidence is presented in Annex 2 of the application and the findings are summarised below. There are few data exploring the effectiveness of gatifloxacin in MDR-TB in conventional 24 month regimens and shorter MDR-TB regimens. Four observational studies were presented (5-8); all were assessed as 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 to 64.9% for regimens without gatifloxacin (relative benefit not estimable; absolute effect 191 more successes per 1000; 95% CI 116 to 265 more). Deaths among patients on 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 to 99 fewer).
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 drugs stopped due to adverse effects) were reported in 3.6% of gatifloxacin-treated patients compared to 8% of treatments not including 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 parent company to stop manufacture 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, impacting negatively 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 to gatifloxacin (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), prothionamide (or ethionamide) and clofazimine for four months (prolonged to six months in case of failure of sputum conversion), followed by a continuation phase of pyrazinamide, ethambutol, gatifloxacin (or moxifloxacin), and clofazimine for five months. Since May 2016, WHO recommends the shorter MDR-TB regimen in selected patients; gatifloxacin could thus have a central role in a regimen which 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 is usually composed of pyrazinamide plus at least 4 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 prothionamide), 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. Following a review of evidence which accrued from such studies, in May 2016 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

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	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 TB medicines for which manufacturers will be invited to submit an Expression of Interest for 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 for fluoroquinolones recommended as Group A alternatives in the updated WHO guidelines could be considered.
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 (MDR-TB). The Committee noted that gatifloxacin, in short therapy regimens, did not show superiority in benefit to harm ratio to alternative fluoroquinolones currently listed on the EML and EMLc (levofloxacin and moxifloxacin).

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1. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update Geneva: World Health Organization; 2016. Available from: http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/.
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3. Global tuberculosis report 2016 Geneva: World Health Organization; 2016. Available from: http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf?ua=1.
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Isoniazid + pyrazinamide + rifampicin – new formulation– EMLc
Isoniazid + rifampicin – new formulation – EMLc

Isoniazid + pyrazinamide + rifampicin **Isoniazid + rifampicin**	**ATC Code: J04AM05** **ATC Code: J04AM02**
Proposal:	The application requested addition of two fixed-dose combination (FDC), 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) to the core list of the EMLc.
Applicant:	Dr Malgorzata Grzemska, Dr Kefas Samson and Ms Annemieke Brands, WHO Global TB Program.
WHO Technical Department:	Global TB Program
EML / EMLc	EMLc
Section:	6.2.4 Antituberculosis medicines
Dose form(s) & strengths(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, eg. resubmission, previous EC consideration)	A 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 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 for the treatment of children with tuberculosis on the EMLc. FDCs containing isoniazid, pyrazinamide and rifampicin in different strengths to 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, there were 210,000 childhood deaths due to tuberculosis, including 40,000 children co-infected 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 concluded 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 25kg, 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 (UNOPS)
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 favourable benefits including appropriate dosing, ease of administration and reduced pill burden and could contribute to better therapeutic adherence.

References:

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2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2009 (including the 16th WHO Model List of Essential Medicines and the 2nd WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2009. (WHO Technical Report Series, No. 958).
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4. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd edition. Geneva: World Health Organization; 2014.
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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:	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) & strengths(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 MDR-TB, based on availability and programme considerations. Ofloxacin does not have an individual listing for this indication: *levofloxacin**: ***Tablet:*** *250mg; 500 mg; 750 mg.* ** Ofloxacin and moxifloxacin may be alternatives based on availability and programme considerations.*
Public health relevance: (burden of disease)	It is estimated that there are 580,000 patients who develop rifampicin-resistant or MDR-TB globally each year and who would need second-line TB treatment regimens to increase their 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 of this process, a reclassification of medicines for inclusion in regimens for rifampicin-resistant or multidrug-resistant tuberculosis was recommended. The new guidance no longer recommends ofloxacin among the fluoroquinolone options. This is because the other members of the fluoroquinolone class listed (levofloxacin, moxifloxacin and gatifloxacin) are more effective agents in second-line TB regimens than ofloxacin. The three fluoroquinolones now recommended have become more widely available and affordable globally in recent years. No specific data wereprovided 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 provides a summary of the evidence for use of later generation fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) compared to ofloxacin for adults with rifampicin-resistant or multidrug-resistant tuberculosis (3). Ahuja et al (4) used individual patient data meta-analysis from 32 observational studies that assessed treatment success versus failure/relapse/death in patients on later generation fluoroquinolones or ofloxacin as part of a MDR-TB regimen. Treatment success was reported as 83% for regimens with later generation fluoroquinolones compared to 73.2% for regimens including ofloxacin (OR 1.9; 95% CI 1.0 to 3.6) (low quality evidence). Serious adverse events attributable to fluoroquinolones have been reported as 2.8% (95% CI 1.9% to 4.1%) with ofloxacin or ciprofloxacin, compared to 1.2% (95% CI 0.6% to 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/prothionamide, 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-clavulanate, 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 (MDR-TB).

References:

1. Global tuberculosis report 2016 Geneva: World Health Organization; 2016. Available from: http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf?ua=1.
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4. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

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Streptomycin – deletion – EML and EMLc

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:	Malgorzata Grzemska, WHO Global TB Programme.
WHO Technical Department:	Global TB Programme
EML / EMLc	EML
Section:	6.2.4 Antituberculosis medicines
Dose form(s) & strengths(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, eg. 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 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 multi-drug resistant (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 multidrug-resistant tuberculosis (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 anti-tuberculosis 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 MDR-TB.

References:

Nil.

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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 *Talaromyces marneffei* in AIDS patients.
Applicant:	Global Action Fund for Fungal Infection, in association with the International Foundation for Dermatological Societies, Manchester University and the Medical Mycology Reference Laboratory of the Instituto de Salud Carlos III.
WHO Technical Department:	N/A
EML / EMLc	EML and EMLc
Section:	6.3 Antifungal medicines
Dose form(s) & strengths(s):	Capsule: 100 mg Oral liquid: 10 mg/mL
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 interior 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 over 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. 5-year survival without antifungal treatment is approximately 20% (3, 4). It is estimated that over 200,000 people develop acute invasive aspergillosis annually (5). The disease is common in people with acute leukaemia, stem cell (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 transplanted patients, 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 extremes of age and the immunosuppressed. Chronic cavitary

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	histoplasmosis is a rare complication of histoplasmosis with patients with chronic obstructive pulmonary disease at risk (10). Sporotrichosis has been reported worldwide, but with most cases reported from central and south America and China (11, 12) with rates of 1 case per 1000 in hyperendemic rural areas. The infecting fungus, *S. schenckii,* usually enters the body through traumatic implantation. Disease may become disseminated in patients with AIDS. Paracoccidioidomycosis is endemic to Latin America and 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 co-infection 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 Hong Kong and around 30% of patients in northern Thailand are affected (15). It is known to affect other immunocompromised patients and is a potentially fatal infection if untreated (16). Chromoblastomycosis is characterised 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 by Agarwal et al. (18) compared itraconazole with supportive therapy in 31 patients with chronic cavitary pulmonary aspergillosis. Response to therapy was assessed clinically, radiologically and overall following 6 months 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 demonstrating clinical and radiological response were also higher in the itraconazole group. Acute invasive aspergillosis (20, 21) A multicentre prospective, uncontrolled study by Denning et al. (21) investigated oral itraconazole in 76 evaluable patients with various underlying conditions. Response was based on clinical and radiological criteria and categorised 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. 26% of patients discontinued therapy due to clinical worsening or death due to aspergillosis. 30% of patients withdrew due to 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 a 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 28.8% with placebo. (p=0.004). Prophylaxis significantly decreased 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/ mm^3. Sporotrichosis Three prospective, uncontrolled multi-centre studies evaluated itraconazole in patients with cutaneous, systemic and lymphangitic sporotrichosis (25-27). High or complete rates of response to itraconazole were reported in all three studies. Paracoccidioidomycosis A retrospective cohort study compared itraconazole with trimethoprim+sulfamethoxazole (TMP-SMX) in 200 patients with mild or moderate paracoccidioidomycosis (28). There was a higher incidence of response with itraconazole compared to TMP-SMX, with cure rates of

	86.4% and 51.3%, respectively. In addition, the median treatment period for itraconazole was significantly shorter than for TMP-SMX: 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 TMP–SMX. 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 a 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 F. pedrosoi (31, 32). At a dose of 200-400 mg itraconazole per day, 42% of patients (having mild to moderate disease) achieved a clinical and biological cure after a mean duration of therapy of 7.2 months (3.2-29.6 months). Clinical improvement was observed in 21% (having severe lesions) after a mean duration of treatment of 17.6 months (10.7-22.5 months). In total, 12 (63%) out 19 patients benefited from itraconazole treatment (31). In a small study of 10 patients administered 100-200 mg itraconazole per day, after 12 months of treatment 90% of patients demonstrated benefit (cure, major improvement or minor improvement) (32). Itraconazole is included as a recommended (or alternative) treatment for the proposed infections in international guidelines as summarized in Tables 12 and 13 of the application (33-36).
Summary of evidence: harms (from the application)	Known adverse events associated with itraconazole include gastro-intestinal 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 potentially results in an inability to achieve therapeutic serum concentrations (38). In addition, many clinically significant interactions relate to the suppression of CYP3A4 activity by itraconazole that leads to higher exposures of agents that are metabolised via this route. Itraconazole also prolongs the action of midazolam, digoxin, cyclosporine, 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 capsule and liquid 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, whereas this 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 as US$ 6.73. Costs were estimated in the application to range from less than US$ 0.01 in Zambia and Sri Lanka to US$ 102 in Sweden.
Availability:	Widely available, including generics.

Other considerations:	With regard to therapeutic drug monitoring (TDM), the Expert Committee considered that where TDM is available, it may help inform management considerations, especially to prevent under dosing. However, in severe infections, 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 on 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 Talaromyces marneffei in AIDS patients. The Committee did not recommend the inclusion of the indication of treatment for 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:	Global Action Fund for Fungal Infection, in association with the International Foundation for Dermatological Societies, Manchester University and the Medical Mycology Reference Laboratory of the Instituto de Salud Carlos III.
WHO Technical Department:	N/A
EML / EMLc	EML and EMLc
Section:	6.3 Antifungal medicines
Dose form(s) & strengths(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, eg. 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 does not have 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 over 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. 5-year survival without antifungal treatment is approximately 20% (2, 3). It is estimated that over 200,000 people develop acute invasive aspergillosis annually (4). The disease is common in people with acute leukaemia, stem cell (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 transplanted patients, the number of individuals with invasive aspergillosis may be higher than estimated. Mortality without antifungal treatment is 100%.

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Summary of evidence: benefits (from the application)	The application summarized the outcomes of prospective studies of voriconazole in chronic and invasive pulmonary aspergillosis. <u>Chronic pulmonary aspergillosis:</u> Cadranel et al. evaluated the efficacy and safety of voriconazole in a prospective, open, multicenter trial of 41 minimally or non-immunocompromised patients with proven CPA (8). The primary endpoint 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 % 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 %. <u>Acute invasive aspergillosis:</u> Herbrecht et al. compared voriconazole and amphotericin B as primary therapy for invasive aspergillosis in 277 treated patients in a randomized, unblinded trial (9). Most patients had underlying allogeneic hematopoietic-cell transplantation, acute leukemia, or other hematologic diseases. At week 12, for the modified intention to treat population, a complete or partial response to therapy ("a 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 to 32.9). The 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 to 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 by Patterson et al. followed the same population enrolled in the trial by Herbrecht et al. and reported the outcomes of patients who switched from voriconazole or amphotericin B to other licensed antifungal therapies (OLAT) (10). 36% of voriconazole treated patients switched to OLAT, compared with 80% of OLAT treated patients. Switches were made because of intolerance or insufficient response in 70% and 24% of the amphotericin B and voriconazole 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 chronic pulmonary aspergillosis in adults and children (strong recommendation, high-quality evidence) (11, 12).

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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, and diarrhea, 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, hypokalemia, and concomitant medications (e.g., quinolones) that may be contributory. Reversible central and peripheral neurologic symptoms and hallucinations may be observed in association with higher drug concentrations but with significant variability; these may be confused with other aetiologies of CNS dysfunction. Voriconazole concentrations may be a predictor of CNS neurotoxicity, which is reversible. Peripheral neuropathy may occur after months of therapy, usually sensory, sometimes motor or mixed, and is related to increased doses required to achieve adequate plasma concentrations. Prolonged use of voriconazole (e.g., for osteomyelitis or meningitis) or prophylaxis has revealed newer toxicities including periostitis with severe pain in bones or joints in association with elevated serum fluoride levels. The risk for squamous cell skin cancer or melanoma in sun-exposed areas is enhanced by concomitant immunosuppression and chronic voriconazole use, especially in fair- skinned persons (11). Voriconazole is metabolized via CYP3A4, CYP2C9 and CYP2C19 pathways and is thus associated with a number of drug-drug interactions including (but not limited to) selected antiretroviral medicines, rifampicin, antiepileptic medicines, cyclosporine, HMG CoA reductase inhibitors, 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 as a result prices are changing in many countries, but generally remain high. Daily treatment costs for oral voriconazole are described to vary from US$ 2.08 in Pakistan to US$ 94.00 in Thailand.
Availability:	Widely available.
Other considerations:	With regard to therapeutic drug monitoring (TDM), the Expert Committee considered that where TDM is available, it may help inform management considerations, especially to prevent under dosing. However, in severe infections, 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 on 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 treatment of 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.

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6.4 Antiviral medicines

6.4.2 Antiretrovirals

ARV formulations for deletion from 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:	1. Dr Marco Vitoria, WHO Department of HIV/AIDS (various) 2. 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 (and sub-sections)
Dose form(s) & strengths(s):	Various
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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

The WHO HIV department 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 WHO *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

UNDER REVISION

Summary of evidence: benefits
(from the application)

WHO HIV Department 2017 update:
The rationale provided in the application for the requested new deletions fell into three categories, described below and summarised 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 WHO Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Their Children. To achieve alignment with the formulation recommendations of the recently revised formulary from the IATT (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 mesilate)	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 the clinical use of the protease inhibitor (PI) 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 PIs, saquinavir is associated with QT prolongation and a requirement for ECG monitoring. Numerous alternative PIs (+/- 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. A 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 50mg/mL oral liquid and 50 mg dispersible tablets. Saquinavir: Numerous alternative protease inhibitors (+/- ritonavir in FDC) are available on the EML. Zidovudine: Only parenteral HIV dose form on the EML. Multiple alternative oral dose forms available, including in FDC.
Other considerations:	No applications were received to support retention of any of the medicines flagged for deletion in 2015, with the exception of the HIV Department's request to retain lamivudine oral liquid on the EMLc.
Committee Recommendation: **(draft for EC consideration)**	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 HIV department of the continued recommendation in current WHO guidelines for use of lamivudine oral liquid for the treatment of newborns, the Expert Committee recommended 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 therefore considered at high risk for maternal-to-newborn HIV transmission. The Committee therefore recommended zidovudine solution for IV infusion injection be retained on the EML at this time for the subset of HIV positive pregnant patients that are at high risk of transmitting the infection to their newborns.

References:

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5rd WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015. (WHO Technical Report Series, No. 994).
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. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/.
3. Policy Brief: IATT Paediatric ARV Formulary and Limited-Use List - 2016 Update: Interagency Task Team (IATT) for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children; 2016. Available from: http://emtct-iatt.org/wp-content/uploads/2016/10/Updated-Ped-ARV-Formulary-List-5-Sept-2016-1.pdf.

UNEDITED VERSION

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

Abacavir – addition of 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:	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) & strengths(s):	Tablet: 60 mg (dispersible, scored)
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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/5mL is currently the only formulation of abacavir included on the 5th EMLc (2015). It has been recommended for deletion in 2017 in accordance with the 2015 Expert Committee recommendation.
Public health relevance: (burden of disease)	150,000 new paediatric HIV infections occurred in 2015, with 1.8 million children now living with HIV (1). There is evidence that over 50% of infected infants will progress to AIDS and death by age 2 years without antiretroviral treatment (2). Age-appropriate dosage forms for use in infants and children are necessary to successfully scale-up treatment of 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 by the WHO Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children for use in children less than 3 years of age who are undergoing tuberculosis treatment and require a triple nucleoside ART regimen (3). The application described a review of abacavir use in paediatric patients by Melroy et al., which found that there was benefit in terms of increased antiretroviral activity of a triple NRTI regimen containing zidovudine, lamivudine and abacavir compared with zidovudine, lamivudine and placebo (4). The application also described findings of the ARROW study that viral load suppression was similar to standard NNRTI-based ART at 48 weeks for children co-infected with TB who moved to a triple-NRTI regimen containing abacavir, and was significantly lower at 144 weeks (5). Advantages of a dispersible tablet formulation over syrups include easier and lower-cost transport, lower production costs, able to be used in very young children and may be dispersed in breast milk or formula. Scored tablets provides for 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 3-10 years of age (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 (PPPY) for abacavir dispersible tablets is US$95, compared with a PPPY of US$135 for abacavir oral liquid. The application also claimed cost savings in terms of reduced shipment, storage and wastage costs.
Availability:	Cipla Limited, India Abacavir 60 mg dispersible tablets are included on WHO List of Prequalified Medicinal Products.
Other considerations:	N/A
Committee Recommendation:	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 dispersible, scored tablet formulation of abacavir 60 mg to the core list of the EMLc, noting the importance of the availability of effective, age-appropriate paediatric dosage forms of antiretroviral medicines. The Committee acknowledged the advantages of dispersible tablets over liquid formulations include easier logistics, lower production costs, and their suitability for use in very young children. Scored tablets also allow greater dosing flexibility across age and weight ranges.

References:

1. UNAIDS, Joint United Nations Programme on HIV/AIDS. AIDS by the numbers - AIDS is not over, but it can be.2016. Available from: http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers.
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):1236-43.
3. Policy Brief: IATT Paediatric ARV Formulary and Limited-Use List - 2016 Update: Interagency Task Team (IATT) for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children; 2016. Available from: http://emtct-iatt.org/wp-content/uploads/2016/10/Updated-Ped-ARV-Formulary-List-5-Sept-2016-1.pdf.
4. Melroy J, Nair V. The antiviral activity, mechanism of action, clinical significance and resistance of abacavir in the treatment of pediatric AIDS. Curr Pharm Des. 2005;11(29):3847-52.
5. Kekitiinwa A, Cook A, Nathoo K, Mugyenyi P, Nahirya-Ntege P, Bakeera-Kitaka S, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. Lancet. 2013;381(9875):1391-403.
6. 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. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/.

UNEDITED VERSION

Zidovudine (ZDV or AZT) – addition of 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:	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) & strengths(s):	Tablet (dispersible, scored): 60 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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)	150,000 new paediatric HIV infections occurred in 2015, with 1.8 million children now living with HIV (1). There is evidence that over 50% of infected infants will progress to AIDS and death by age 2 years without antiretroviral treatment (2). Age-appropriate dosage forms for use in infants and children are necessary to successfully scale-up treatment of 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 WHO Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children for use in children less than 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 NNRTI-based ART at 48 weeks for children co-infected with TB who moved to a triple-NRTI regimen containing zidovudine, and significantly lower at 144 weeks (4). Advantages of a dispersible tablet formulation over syrups include easier and lower-cost transport, lower production costs, able to be used in very young children and may be dispersed in breast milk or formula. Scored tablets provides 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 3-10 years of age (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 (PPPY) for zidovudine dispersible tablets is US$40, compared with a PPPY of US$89 for zidovudine oral liquid. The application also claims cost savings in terms of reduced shipment, storage and wastage costs compared with oral liquid.
Availability:	Sun Pharmaceutical Industries Limited, India Zidovudine 60 mg dispersible tablets are included on WHO List of Prequalified Medicinal Products.
Other considerations:	Weight restriction > 3kg
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 dispersible, scored tablet formulation of zidovudine 60 mg to the core list of the EMLc, noting the importance of the availability of effective, age-appropriate paediatric dosage forms of antiretroviral medicines. The Committee acknowledged the advantages of dispersible tablets over liquid formulations include easier logistics, lower production costs, and their suitability for use in very young children. Scored tablets also allow greater dosing flexibility across age and weight ranges.

References:

1. UNAIDS, Joint United Nations Programme on HIV/AIDS. AIDS by the numbers - AIDS is not over, but it can be.2016. Available from: http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers.
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):1236-43.
3. Policy Brief: IATT Paediatric ARV Formulary and Limited-Use List - 2016 Update: Interagency Task Team (IATT) for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children; 2016. Available from: http://emtct-iatt.org/wp-content/uploads/2016/10/Updated-Ped-ARV-Formulary-List-5-Sept-2016-1.pdf.
4. Kekitiinwa A, Cook A, Nathoo K, Mugyenyi P, Nahirya-Ntege P, Bakeera-Kitaka S, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. Lancet. 2013;381(9875):1391-403.
5. 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. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/.

UNEDITED VERSION

6.4.2.3 Protease inhibitors

Atazanavir + ritonavir – addition – EML

Atazanavir + ritonavir	**ATC Code: J05ARxx**
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:	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) & strengths(s):	Tablet (heat stable): 300 mg (as sulfate) + 100 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Atazanavir 300 mg tablets and ritonavir 100 mg tablets are both currently included individually on the EML.
Public health relevance: (burden of disease)	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% 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 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 which evaluated virologic and immunologic 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 virologic 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, warnings and precautions, drug interactions and precautions for special populations associated with atazanavir and ritonavir, with reference to the U.S. 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, a lower incidence of AIDS-defining illness, a greater 12-month increase in CD4 cell count, and a smaller risk of virologic failure at 12 months for ritonavir boosted atazanavir compared with ritonavir boosted lopinavir. The hazard ratios for ATZ/r versus LPV/r were significantly lower: HR 0.70, 95% CI 0.53 to 0.91 for death, HR 0.67 (95%CI 0.55 to 0.82) for AIDS-defining illness or death and HR 0.91, (95% CI 0.84 to 0.99) for virologic failure at 12 months. The mean 12-month increase in CD4 count was 8.15 (95% CI) -0.13 to 16.43) cells/microL (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. Compared to LPV/r, ATV/r has advantages such a lower pill burden with once daily dosing, and better gastrointestinal tolerability. Disadvantages compared to LPV/r include the incidence of hyperbilirubinaemia, dyslipidaemia and

	contraindication with rifampicin-containing tuberculosis regimens.
Costs / cost-effectiveness:	The average reported price per patient per year (PPPY) for ATV/r FDC 300 mg/100 mg tablets is US$203, compared with a PPPY of US$251 for the component medicines supplied separately. The application also claims cost savings associated with procuring fewer packs, and the advantage of simplifying country supply chain management with consolidation around a single FDC product.
Availability:	Mylan Pharmaceutical Private Limited, India ATV/r 300mg (as sulfate)/100mg tablets are included on WHO's List of Prequalified Medicinal Products.
Other considerations:	N/A
Committee Recommendation: **(draft for EC consideration)**	The Expert Committee recommended the addition of the FDC 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 an NRTI backbone. Compared to LPV/r, and the component medicines given concurrently, the ATV/r FDC has advantages such a reduced pill burden with once daily dosing, and better GI tolerability. The Committee considered that based on the application and additional evidence (documented above), ATV/r may also provide some advantages over LPV/r in terms of efficacy. The Committee considered the availability of FDC ART formulations offer favourable benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

References:

1. UNAIDS, Joint United Nations Programme on HIV/AIDS. AIDS by the numbers - AIDS is not over, but it can be.2016. Available from: http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers.
2. Akanmu AS, Adeyemo T, Lesi F, Bello FO, Okwuegbuna K, Oloko K, et al. Immunological and Virological Outcomes of Patients Switched from LPV/r to ATV/r-Containing Second- Line Regimens. Curr HIV Res. 2015;13(3):176-83.
3. Cain LE, Phillips A, Olson A, Sabin C, Jose S, Justice A, et al. Boosted lopinavir- versus boosted atazanavir-containing regimens and immunologic, virologic, and clinical outcomes: a prospective study of HIV-infected individuals in high-income countries. Clin Infect Dis. 2015;60(8):1262-8.
4. 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. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/.

UNEDITED VERSION

Lopinavir + ritonavir – new formulation and strength – EMLc

Lopinavir + ritonavir	**ATC Code: J05AR10**
Proposal:	The application requested addition of a new formulation of lopinavir + ritonavir (LPV/r) fixed dose combination to the core list of the EMLc for the treatment of children with HIV infection.
Applicant:	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) & strengths(s):	Capsule (containing oral pellets): 40 mg + 10 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	LPV/r has been included on the EMLc since 2007. Currently listed formulations are oral liquid (400 mg + 100 mg/5mL) and heat stable tablets (100 mg + 25 mg).
Public health relevance: (burden of disease)	150,000 new paediatric HIV infections occurred in 2015, with 1.8 million children now living with HIV (1). There is evidence that over 50% of infected infants will progress to AIDS and death by age 2 years without antiretroviral treatment (2). Age-appropriate dosage forms for use in infants and children are necessary to successfully scale-up treatment of 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 provides brief summaries of the results of the two randomized controlled trials (3, 4) upon which the decision 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) was made. The application also describes 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 to 12 months and 1 to 4 years, LPV concentrations and pharmacokinetic parameters were slightly higher with pellets compared with liquid formulation. For the cohort of older patients (4 to 13 years), LPV concentrations were higher with paediatric tablets compared with pellets. In the cohort of 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 group considered that the LPV/r pellet formulation can offer advantages in resource limited settings where challenges exist with 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 U.S. product label.
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* make the following recommendations in relation to LPV/r: A 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 exposure. If LPV/r is not feasible,

	treatment should be initiated with an NVP-based regimen (strong recommendation, moderate quality evidence). After failure of a first-line NNRTI-based regimen, children should be switched to a boosted PI-based regimen. LPV/r or ATV/r are preferred (conditional recommendation, very low-quality evidence).(9)
Costs / cost-effectiveness:	The average reported price per patient per year (PPPY) for LPV/r pellets is US$467, compared with a PPPY of US$150 or US$100 for the oral solution or tablets, respectively. The application states that although more expensive, the pellets represent an alternative to address the challenge of implementing the recommendation of LPV/r as first line treatment for all patients under 3 years of age in low resource settings due to the lack of a heat-stable, child-friendly formulation. The application describes cost savings associated with shipment, freight and storage compared with the oral solution.
Availability:	Cipla Ltd, India
Other considerations:	N/A
Committee Recommendations: **(draft for EC consideration)**	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 noted that LPV/r-based regimens are recommended in current WHO HIV treatment guidelines as first-line ART for all children infected with HIV younger than 3 years of age, regardless of NNRTI exposure. LPV/r-based regimens are also a preferred treatment option for children who have failed first-line NNRTI-based regimens. The Committee also noted the findings of the CHAPAS-2 study that oral pellets were more acceptable, and concentrations and pharmacokinetic parameters were slightly higher in younger children compared to oral solution. The oral pellet formulation also has advantages over the oral solution in terms of logistics, storage and less wastage. The Committee considered that that age-appropriate FDC ART formulations such as this one offer favourable benefits including greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

References:

1. UNAIDS, Joint United Nations Programme on HIV/AIDS. AIDS by the numbers - AIDS is not over, but it can be.2016. Available from: http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers.
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):1236-43.
3. Palumbo P, Lindsey JC, Hughes MD, Cotton MF, Bobat R, Meyers T, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. N Engl J Med. 2010;363(16):1510-20.
4. Violari A, Lindsey JC, Hughes MD, Mujuru HA, Barlow-Mosha L, Kamthunzi P, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012;366(25):2380-9.
5. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. Available from: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf.
6. Kekitiinwa A, Musiime V, Thomason MJ, Mirembe G, Lallemant M, Nakalanzi S, et al. Acceptability of lopinavir/r pellets (minitabs), tablets and syrups in HIV-infected children. Antivir Ther. 2016;21(7):579-85.
7. Musiime V, Fillekes Q, Kekitiinwa A, Kendall L, Keishanyu R, Namuddu R, et al. The pharmacokinetics and acceptability of lopinavir/ritonavir minitab sprinkles, tablets, and syrups in african HIV-infected children. J Acquir Immune Defic Syndr. 2014;66(2):148-54.

UNEDITED VERSION

8. Policy Brief: IATT Paediatric ARV Formulary and Limited-Use List - 2016 Update: Interagency Task Team (IATT) for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children; 2016. Available from: http://emtct-iatt.org/wp-content/uploads/2016/10/Updated-Ped-ARV-Formulary-List-5-Sept-2016-1.pdf.
9. 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. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/.

UNEDITED VERSION

6.4.2.4 Integrase inhibitors

NEW SUB-SECTION

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 (NNRTI)- or protease inhibitor (PI)-based regimens.
Applicant:	Dr Marco Vitoria, WHO Department of HIV/AIDS
WHO Technical Department:	WHO Department of HIV/AIDS
EML / EMLc	EML
Section:	New sub-section: 6.4.2.4 Integrase inhibitors
Dose form(s) & strengths(s):	Tablet: 50 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, 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 alternative integrase inhibitor, raltegravir, for second-line treatment.
Public health relevance: **(burden of disease)**	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% 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 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 per mL compared with 76% in the raltegravir group (adjusted mean difference 4.5%, 95% 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 a HIV RNA level of less than 50 copies per mL at 48 weeks (88% versus 81%; adjusted treatment difference 7%, 95% CI 2% to 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 dosed with two NRTIs (4). At 96 weeks, a statistically significantly greater proportion of the dolutegravir group had HIV-1 RNA less than 50 copies per mL (adjusted mean difference 12.4%, 95% CI 4.7% to 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 pre-specified secondary endpoint. At 48 weeks, the proportion of patients in each group with HIV-1 RNA < 50 copies per mL was 71% for dolutegravir versus 64% for raltegravir (adjusted mean difference 7.4%, 95% CI 0.7% to 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 ART was demonstrated to be effective in ART-experienced patients demonstrating integrase inhibitor resistance with 69% of patients with prior virologic failure and resistance to other integrase inhibitors achieving virological suppression at week 24 (6). The IMPAACT P1093 clinical trial of dolutegravir plus two NRTIs in treatment-experienced children and adolescents assessed the pharmacokinetics and efficacy of dolutegravir in treatment experienced adolescents. Among the 12-18 years age cohort, 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 to other antiretrovirals in the abovementioned clinical trials. The most common clinical adverse observed 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 nucleoside reverse transcriptase inhibitor (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 of the efficacy and safety of integrase inhibitors (INSTI, 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 effects, but were better than elvitegravir+cobicistat in terms of viral suppression and treatment discontinuation. Compared with efavirenz 600 mg, dolutegravir has advantages including lower potential for drug interactions, a shorter median time to viral suppression and a 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 with tuberculosis co-infection.
Costs / cost-effectiveness:	The unit price for dolutegravir 50 mg averages US$0.127. In comparison, the average unit price for efavirenz 600 mg is US$0.111. The application claims that with increasing volumes and generic manufacture, the unit price of dolutegravir is expected to decline, and pricing agreements be refined.
Availability:	ViiV Healthcare, United Kingdom; Aurabindo Pharma Limited, India. Generic versions of dolutegravir 50 mg received tentative approval from the FDA 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: GSK have signed an agreement for dolutegravir with MPP
Committee Recommendations: **(draft for EC consideration)**	The Committee noted that dolutegravir is recommended as a first-line ART treatment option in current WHO HIV treatment guidelines, is included on the list of prequalified medicinal products and access could be improved via generic licensing agreements through the Medicines Patent Pool as described during the presentation to the Open Session of the meeting (e.g., nine generic manufacturers have taken generic licences, and three have applied for WHO prequalification).

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	Taking into consideration the evidence of dolutegravir as 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 sub-section for integrase inhibitors.

References:

1. UNAIDS, Joint United Nations Programme on HIV/AIDS. AIDS by the numbers - AIDS is not over, but it can be.2016. Available from: http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers.
2. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013;13(11):927-35.
3. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369(19):1807-18.
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8. 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. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/.

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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 (PI)-based regimen.
Applicant:	Dr Marco Vitoria, WHO Department of HIV/AIDS
WHO Technical Department:	WHO Department of HIV/AIDS
EML / EMLc	EML and EMLc
Section:	New sub-section: 6.4.2.4 Integrase inhibitors
Dose form(s) & strengths(s):	Tablet: 400 mg Tablet (scored): 100 mg Tablet (chewable): 25 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 alternative integrase inhibitor, dolutegravir, as an alternative first-line treatment.
Public health relevance: (burden of disease)	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% 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 antiretroviral therapy in 2015 (1). 150,000 new paediatric HIV infections occurred in 2015, with 1.8 million children now living with HIV (1). There is evidence that over 50% of infected infants will progress to AIDS and death by age 2 years without antiretroviral treatment (2).
Summary of evidence: benefits (from the application)	The application presented the findings of the following studies: Pooled results of the BENCHMARK-1 AND BENCHMARK-2 double-blind, randomized, phase 3 studies of raltegravir in combination with optimized background therapy (OBT) versus OBT alone in patients with HIV who have documented triple-class resistance. At Week 96, 55% of the raltegravir group had achieved virologic suppression (HIV RNA < 50 copies/mL) compared to 27% of the OBT group. The raltegravir group also had greater mean change in CD4 count from baseline than controls (118 cells/mm^3 versus 47 cells/mm^3) (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 a HIV RNA < 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 simples virus infection) or death, a CD4+ count of > 250 cells/mm^3, and a viral load < 10 000 copies per 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 to 18 years. Among patients who received the final recommended dose, 53.7% achieved a 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/mm^3 and 155.7 cells/mm^3 at 24 weeks

	and 48 weeks respectively. Results were consistent across the different age cohorts investigated (6).
Summary of evidence: harms (application)	Raltegravir was well tolerated in the BENCHMARK 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, along 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 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 (PPPY) for raltegravir are reported as US$642 (400 mg), US$426 (100 mg) and US$657 (25 mg). These prices are significantly greater than NRTI and PI alternatives.
Availability:	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 the majority of patients, but that currently no data exist for the use of dolutegravir in these two populations (i.e., pregnant women and children).

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FIXED-DOSE COMBINATIONS

Abacavir + lamivudine – addition of a new strength – EMLc

Abacavir + lamivudine	**ATC Code: J05AR02**
Proposal:	The application requested addition of a new strength formulation of abacavir + lamivudine fixed-dose combination (FDC) tablets to the core list of the EMLc for the treatment of children with HIV infection.
Applicant:	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) & strengths(s):	Tablet (dispersible, scored): 120mg (as sulfate) + 60 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	A different strength formulation of abacavir + lamivudine 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)	150,000 new paediatric HIV infections occurred in 2015, with 1.8 million children now living with HIV (1). There is evidence that over 50% of infected infants will progress to AIDS and death by age 2 years without antiretroviral treatment (2). Age-appropriate dosage forms for use in infants and children are necessary to successfully scale-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 to 10 years of age (conditional recommendation, moderate quality evidence).
Costs / cost-effectiveness:	The average reported price per patient per year (PPPY) for abacavir + lamivudine 120mg + 60 mg dispersible tablets is US$85, compared with a PPPY of US$100 for the 60 mg + 30 mg tablets, and US$172 for oral liquid formulations of abacavir and lamivudine. The application

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	also claims cost savings in terms of reduced shipment, storage and wastage costs.
Availability:	Mylan Laboratories Limited, India Abacavir + lamivudine 120 mg + 60 mg dispersible tablets are included on WHO List of Prequalified Medicinal Products.
Other considerations:	N/A
Committee Recommendations:	The Expert Committee recommended the addition of the new strength of a fixed-dose combination of abavacir + lamivudine to the EMLc. The Committee noted that abacavir + lamivudine is recommended in current HIV treatment guidelines as an NRTI backbone of first-line ART regimens for infants and children under 3 years of age and is the preferred NRTI backbone for children aged 3 to 10 years. The Committee considered that that the availability of age-appropriate FDC ART formulations offer favourable benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

References:

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Cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide – addition – EML

Cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide	**ATC Code: J05AR18**
Proposal:	The application requested addition of a fixed-dose combination (FDC) 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 older. 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:	Gilead Sciences Inc
WHO Technical Department:	WHO Department of HIV/AIDS
EML / EMLc	EML
Section:	6.4.2 Antiretrovirals – FIXED-DOSE COMBINATIONS
Dose form(s) & strengths(s):	Tablet: 150 mg + 150 mg + 200 mg + 10 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	This was the first application seeking listing of COBI + EVG + FTC + 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 Expert Committee considered that the COBI + EVG + FTC +TDF combination demonstrated non-inferiority in terms of efficacy and safety compared with TDF + FTC (or lamivudine, 3TC) + efavirenz (EFZ), 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 a FDC formulation in terms of reducing pill burden and potentially improving adherence, but noted that this FDC had not demonstrated 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 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 (1).
Public health relevance: (burden of disease)	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% 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 antiretroviral therapy 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 1,733 treatment-naive adults with HIV-1 infection. The pooled results of these trials formed the basis for regulatory approval in Europe and the United States. The primary efficacy endpoint in both studies was the proportion of subjects with viral load less than 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 less than 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 to 18 years weighting 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 to 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 antiretroviral treatment 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 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 found to be associated with a smaller decrease in bone mineral density (BMD) at lumber 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 lumber 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 demonstrated improvements 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), 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 EML inclusion 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 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 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 alternative options 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:	Wholesale acquisition costs of the TAF combination in the United states described in the

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	application was US$ 2,577.66 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" to whom only production and related costs are charged. The application stated 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 (GPRM) reports the median treatment cost per year in 2016 for the current preferred first-line ART (TDF + FTC + EFV) as US$ 77.12.
Availability:	Gilead Sciences Inc. This product is currently licensed in Europe, the United States, Canada and Australia. Gilead has licencing agreements with generic drug manufacturers in India, South Africa and China, 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: **(draft for EC consideration)**	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 ARV-naive adults and children aged 12 years and older. The Committee noted the suggestion of a better safety profile associated with the TAF combination compred to the corresponding TDF combination but considered this to be 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 ARV in WHO guidelines. The Committee recalled that a similar TDF-based formulation was not previously recommended for inclusion on the EML in 2015 on the basis of no clinical advantage over currently recommended formulations being demonstrated.

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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 (FDC) formulation of efavirenz + lamivudine + tenofovir disoproxil fumarate (TDF) on the core list of the EML for the treatment of HIV infection in adults and adolescents.
Applicant:	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) & strengths(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, eg. resubmission, previous EC consideration)	The EML currently lists a FDC formulation of efavirenz 600 mg + emtricitabine 200 mg + TDF 300 mg, with annotation that emtricitabine is an acceptable alternative to lamivudine, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals. The intent of this listing should be interpreted to capture formulations comprised of efavirenz 600 mg, lamivudine 300 mg and TDF 300 mg. In effect, this application sought listing of a new strength formulation of efavirenz + lamivudine + TDF.
Public health relevance: (burden of disease)	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% 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 antiretroviral therapy in 2015 (1).
Summary of evidence: benefits (from the application)	The ENCORE1 study was a randomized, double-blind, placebo-controlled non-inferiority trial which compared antiretroviral regimens containing EFV 400 mg or EFV 600 mg in combination with emtricitabine and TDF at recommended doses (2). At week 96, the proportions of patients with viral load less than 200 copies/mL were 90.0% and 90.6% in the 400 mg and 600 mg treatment arms, respectively (difference -0.6; 95% 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 efavirenz, 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 was not statistically significantly different between treatment groups (2).
Additional evidence: (not in the application)	N/A
WHO Guidelines:	EFV400 + 3TC (or 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 inhibitors (INSTI, dolutegravir, raltegravir and elvitegravir+cobicistat) and efavirenz in adult patients with HIV. The review found moderate quality evidence showing comparable effects in terms of viral load suppression between EFV

	400 mg/day and EFV 600 mg/day, and greater effects of EFV400 mg/day in terms of CD4 cell count recovery and 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 with tuberculosis co-infection using rifampicin.
Costs / cost-effectiveness:	The proposed price of EFV400 + 3TC + TDF is US$ 99 per patient per year (PPPY) or up to 8% lower than the EFV600 +3TC + TDF price. The price is to be confirmed once FDA PEPFAR review is completed in early 2017. The FDCs have a higher average cost than their components supplied individually. Moderate overall cost-savings at health system level are claimed in part due to the EFV400 combination having fewer treatment-limiting side effects.
Availability:	Mylan Laboratories Limited, India. The product was granted tentative approval by the US FDA on 10 March 2017 as part of the President's Emergency Plan for AIDS Relief (PEPFAR) drug review program.
Other considerations:	N/A
Committee Recommendations:	The Expert Committee recommended a new formulation of efavirenz + lamivudine + TDF for inclusion in the EML. The Committee noted the favourable benefit to risk profile for the lower-strength efavirenz combination: efavirenz 400 mg combinations were found to be non-inferior to combinations with higher doses (600 mg) of efavirenz in terms of efficacy in ENCORE1, 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 favourable benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

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UNEDITED VERSION

Emtricitabine + tenofovir alafenamide – addition – EML

Emtricitabine + tenofovir alafenamide	**ATC Code: J05AR17**
Proposal:	The application requested addition of a fixed-dose combination (FDC) 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 older, in combination with other antiretroviral agents.
Applicant:	Gilead Sciences Inc.
WHO Technical Department:	WHO Department of HIV/AIDS
EML / EMLc	EML
Section:	6.4.2 Antiretrovirals – FIXED-DOSE COMBINATIONS
Dose form(s) & strengths(s):	Tablet: 200 mg + 10 mg, 200 mg + 25 mg The appropriate TAF dosage is governed by the third agent used in the 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-nucleotide reverse transcriptase inhibitors (NNRTIs), unboosted integrase inhibitors and co-receptor blockers.
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 of FTC with tenofovir disoproxil fumarate (TDF) has been included on the EML since 2007.
Public health relevance: (burden of disease)	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% 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 antiretroviral therapy 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). A summary of the findings of these studies is available in the summary for the COBI+EVG+FTC+TAF application. Bioequivalence between FTC+TAF 200 mg + 10 mg, administered with COBI+EVG, and FTC+TAF 200mg+25mg administered without a pharmacokinetic enhancer and a single-tablet regimen of COBI+EVG+FTC+TAF has been demonstrated (5). Results of switching studies presented in the application suggest efficacy in terms of maintenance of virologic suppression with switching to TAF-containing regimens from TDF-containing regimens (4, 6-8), including in patients with renal impairment, and multi-drug resistant HIV infection.
Summary of evidence: harms (from the application)	Refer to the summary for the COBI+EVG+FTC+TAF application for safety considerations relating to TAF in comparison to TDF.
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 (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI). • TDF + 3TC (or 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 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 alternative options 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:	Wholesale acquisition cost of the FTC + TAF combination in the United States described in the application is US$ 1,466 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" to whom only production and related costs are charged. The application states the price for 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 (GPRM) reports the median treatment cost per year in 2016 for FTC + TDF as US$ 55.10.
Availability:	Gilead Sciences Inc. This product is currently licensed in Europe, the United States and Canada. Gilead has licencing agreements with generic drug manufacturers in India, South Africa and China, 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 compred to 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 ARV in current WHO guidelines.

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Emtricitabine + rilpivirine + tenofovir alafenamide – addition – EML

Emtricitabine + rilpivirine + tenofovir alafenamide	**ATC Code: J05AR19**
Proposal:	The application requested addition of a fixed-dose combination (FDC) formulation of emtricitabine (FTC), rilpivirine (RPV) and tenofovir alafenamide (TAF) to the core list of he EML for the treatment of HIV infection in patients aged 12 years and older who are antiretroviral treatment (ART) naive and have HIV1-RNA less than or equal to 100,000 copies per mL. It is also proposed as replacement ART in patients with viral suppression (HIV1-RNA less than 50 copies/mL) on a stable ART regimen.
Applicant:	Gilead Sciences Inc
WHO Technical Department:	WHO Department of HIV/AIDS
EML / EMLc	EML
Section:	6.4.2 Antiretrovirals – FIXED-DOSE COMBINATIONS
Dose form(s) & strengths(s):	Tablet: 200 mg + 25 mg + 25 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 rilpivirine 25 mg and efavirenz 600 mg. Both treatment groups received a dual NRTI-backbone. The Expert Committee acknowledged that the data presented in the application supported the efficacy of this FDC, but noted that rilpivirine is only indicated for patients with a low viral load (<100,000 copies/mL). The Committee considered that triaging patients according to bassline viral load, or switching regimens after achieving 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 rilpivirine, would not be suitable for patients co-infected 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)	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% 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 antiretroviral therapy 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-inferiority of the rilpivirine 25 mg- and efavirenz 600 mg- containing regimens was supported by the pooled results of the ECHO and THRIVE trials for virologic outcomes at week 96 in patients with baseline viral load less than or equal to 100,000 copies/mL (83.7% versus 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 rilpivirine 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 virologic 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). A summary of the findings of these studies is 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 rilpivirine 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 virologic suppression being maintained with switching to FTC + RPV + TAF from FTC + TDF containing regimens. To date, these results have been reported only as a conference presentation (10).
Summary of evidence: harms (from the application)	Refer to the summary for the COBI+EVG+FTC+TAF application for safety considerations relating to TAF in comparison to TDF. From the ECHO and THRIVE trials, the rilpivirine-treated group had a lower frequency of treatment-related grade 2-4 adverse events (17% versus 33%). The greatest differences between treatment RPV and EFV groups was seen with treatment-related psychiatric adverse events (16% versus 27%) and skin rash (5% versus 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* (11) 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 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 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 alternative options 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:	Wholesale acquisition cost of the FTC + RPV + TAF combination in the United States described in the application is US$ 2,345.87 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" to whom only production and related costs are charged. The application states 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 (GPRM) reports the median treatment cost per year in 2016 for the current preferred first-line ART (TDF + FTC + EFV) as US$ 77.12.
Availability:	Gilead Sciences Inc. This product is currently licensed in Europe and the United States. Gilead has licencing agreements with generic drug manufacturers in India, South Africa and China, 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 (1,500) adults have been treated with FTC + RPV + TAF to date.

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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 patients 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 older who are antiretroviral treatment (ART) naive and have HIV1-RNA less than or equal to 100,000 copies per mL. The Committee noted that the FDC is not recommended as first-line ARV in WHO guidelines., and recalled that a similar TDF-based formulation was not previously recommended for inclusion on the EML in 2015 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 – new indication (pre-exposure prophylaxis) – EML
Emtricitabine + tenofovir disoproxil fumarate– new indication – EML
Lamivudine + tenofovir disoproxil fumarate– new indication – EML

Tenofovir disoproxil fumarate **Emtricitabine + tenofovir disoproxil fumarate** **Lamivudine + tenofovir disoproxil fumarate**	**ATC Code: J05AF07** **ATC Code: J05AR03** **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:	1. WHO Department of HIV/AIDS, Ioannis Hodges-Mameletzis (all medicines) 2. Gilead Sciences Inc. (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) & strengths(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, eg. 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 mother-to-child transmission and post-exposure prophylaxis. 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 decline in 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 the achievement of the milestone agreed by the UN General Assembly in 2016 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), as a prevention choice for individuals at substantial risk of HIV infection as part of combination prevention approaches, based on clinical trial evidence supporting efficacy of TDF for use as PrEP across a variety of settings and populations. This recommendation was made available on an early-release basis, in advance of the 2016 revised consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 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 national standards for HIV prevention and treatment keep pace with scientific developments (3).

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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 RCTs and three observational, open-label extension cohort studies) of over 15,000 participants to investigate the effectiveness of PrEP using TDF either alone or in combination with FTC in people at substantial risk of HIV infection (4). Study populations included serodiscordant couples, people who inject drugs, men who have sex with men, female sex workers, transgender women, 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 to placebo. There was a 51% reduced risk of HIV infection associated with PrEP (TDF +/- FTC) across populations (risk ratio (RR) 0.49; 95% CI 0.33 to 0.73, p=0.001). In studies that measured adherence, PrEP was found to be most efficacious at reducing risk of HIV infection in the sub-group with high (≥70% drug detection) adherence (RR 0.30; 95% CI 0.21 to 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 to 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 to 0.86, p=0.001) and FTC+TDC (RR 0.51; 95% CI 0.31-0.83, p=0.007). Two RCTs compared PrEP to 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 to 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 (5) and the Partners PrEP (6) studies. Both of these studies 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 to placebo (hazard ratio (HR) 0.56; 95% CI: 0.37 to 0.85, p=0.005). Efficacy was shown to be related to adherence with patients with detectable study-drug levels having a relative risk reduction of 92% (95% CI 40% to 99%, p<0.001) (5). The Partners PrEP study compared PrEP using TDF alone, FTC+TDF and placebo in 4,747 HIV-serodiscordant heterosexual couples in Kenya and Uganda. Compared to 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 to 0.56, p<0.001) and FTC+TDF (HR 0.25; 95% CI 0.13 to 0.45, p<0.001). The difference between TDF and FTC+TDF with regard to HIV-protective effects was not significantly different (6).
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 (4). 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 to 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 to 1.13, p=0.76). There were no increases in sexual risk behaviour, pregnancy-related adverse events or hormonal contraception effectiveness associated with PrEP. Participants randomized to PrEP had higher risk of developing TDF or FTC resistance compared to placebo among those infected with HIV at commencement of therapy (RR 3.34; 95% CI: 1.11 to 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 life-long ART. The risk of drug resistance due to ART is likely to be greater than the risk of drug resistance due to PrEP (7). The application from Gilead Sciences described the known adverse effects of FTC+TDF on renal and bone health, and the events that occurred with greater frequency in FTC+TDF treated patients in the RCTs and open-label extension trials (nausea, headache, weight loss). The

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	application noted the findings in a meta-analysis by Fonner et al which are the published results of the WHO-commissioned review described above (8).
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* (9) 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 to offer PrEP are likely to vary based on local considerations such as epidemiological factors, available resources, cost, feasibility and demand.
Costs / cost-effectiveness:	The application from the WHO Department of HIV/AIDS summarises the costs of TDF-containing PrEP products in LMICs as follows: **Dose and Pricing of generic ARVs for use in PrEP** **Product** / **Dose(s)** / **Prior Use in PrEP clinical trials** / **FPP Pricing (median/Unit; USD$ per year)** / **API Pricing (Median/Kg; USD$; % of FPP price)** TDF (30 count) / 300 mg / Yes / $45.24 / $170; (41.3%) TDF/FTC (30 count) / 300 mg; 200 mg / Yes, most PrEP data is from this product / $67.20 / $170; $250; (55%) TDF/3TC (30 count) / 300 mg; 300 mg / No data available / $50.48 / $170; $135; (66.5%) The HIV incidence threshold for cost-saving implementation of PrEP will vary depending on the relative costs of PrEP versus HIV treatment, and the expected effectiveness of PrEP. A systematic review of cost-effectiveness studies of PrEP concluded that providing PrEP to populations at highest risk of HIV exposure was the more cost-effective strategy (10). From the Gilead application, the wholesale acquisition cost of FTC + TDF in the United States is US$ 1,466 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" to whom only production and related costs are charged. The application states 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 (GPRM) reports the median treatment cost per year in 2016 for FTC + TDF as US$ 55.10.
Availability:	There are multiple manufacturers of TDF-containing products for PrEP. Many have 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 (FTC) + TDF (and lamivudine (3TC) + 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 SUB-SECTION

Isoniazid+pyridoxine+sulfamethoxazole+trimethoprim – addition – EML and EMLc

Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**ATC Code: N/A**
Proposal:	The application requested addition of a fixed-dose combination (FDC) formulation of isoniazid (INH), pyridoxine (vitamin B6), sulfamethoxazole and trimethoprim (co-trimoxazole, CTX) to the core list of EML and EMLc for the prevention of infections in adults and children living with HIV/AIDS.
Applicant:	Dr Marco Vitoria, WHO Department of HIV/AIDS
WHO Technical Department:	WHO Department of HIV/AIDS
EML / EMLc	EML and EMLc
Section:	New sub-section 6.4.2.5: Medicines for prevention of HIV-related opportunistic infections
Dose form(s) & strengths(s):	Tablet (scored): 300 mg + 25 mg + 800 mg +160 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	WHO included this fixed-dose combination of isoniazid, pyridoxine, sulfamethoxazole, and trimethoprim 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 co-trimoxazole preventive therapy (CPT) and isoniazid preventive therapy (IPT) as part of the standard package of care available to prevent tuberculosis, toxoplasmosis, pneumocystis, bacterial pneumonia, malaria, and isosporiasis; and reduce mortality and hospitalizations among adults and children living with HIV/AIDS (PLHIV) on the condition that active tuberculosis (TB) has been excluded (1). Pyridoxine is recommended in all HIV-infected persons on isoniazid to prevent peripheral neuropathy and other isoniazid toxicities.
Public health relevance: (burden of disease)	HIV infection increases the risk of tuberculosis 20-37-fold, depending on the severity of the HIV epidemic (2). WHO estimated overall 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 was 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 over a period of many years. The INH/B6/ CTX FDC has been used as part of a clinical trial (the REALITY study) conducted in 1805 African patients, including 72 pediatric patients (5 through 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) was conducted to evaluate whether an enhanced package of infection prophylaxis at time of ART initiation would reduce mortality in an African population. The study randomized ART-naïve HIV-infected adults and children aged 5 years and older with CD4< 100 cells/mm^3 to initiating ART with enhanced prophylaxis (continuous co-trimoxazole plus 12 weeks isoniazid/pyridoxine (anti-tuberculosis) and fluconazole (anti-cryptococcal/candida), 5 days azithromycin (anti-bacterial/protozoal) and single-dose albendazole (anti-helminth)), 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 (> 5 years of age) with CD4<100 cells/mm^3 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 decreased 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 pediatric patients enrolled in the study makes it difficult to interpret efficacy results in patients 5 to 17 years of age but the available data support use of the half-dose in patients less than 12 years of age and at weighing least 14 kg and use of the full dose in patients 12 to 17 years of age. In a review and commentary published in 2015, Harries and colleagues summarized the need for a fixed dose combination 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 tuberculosis in settings of high tuberculosis transmission, but long-term treatment is needed to maintain ongoing benefits. They found no evidence to suggest IPT increased the risk of INH-resistant TB. In addition, they noted CPT reduced death by 60% if started with ART at CD4 counts at 350 cells/µL or lower regardless of geographic region. They note the benefits of continuing CPT were further supported by a randomized trial in Uganda and Zimbabwe of children infected with HIV, showing that those who continued CPT after 2 years of ART had reduced admissions to hospitals from 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 decreasing pill burden. There are a number of relevant drug interactions with the medicines included in the FDC. However these apply to the medicines administered separately as well. No specific safety issues associated with INH/B6/CTX FDC that would preclude its use are expected to pose a differential risk in the international health setting.
Additional evidence: (not in the application)	A systematic review 10 RCTs (7 619 patients) comparing IPT to placebo in HIV-infected adults found IPT was associated with a reduced risk of TB among all participants (relative risk (RR) 0.65; 95% 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 (1 476 patients) comparing CTP versus placebo in HIV infected adults found CTP to be 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 to 0.9), and hospitalization (RR=0.66; 95% CI 0.48 to 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 co-trimoxazole preventive therapy (CPT) for adults, CPT for HIV-infected infants, children and adolescents and preventing TB disease in patients at high risk. The guidelines note that all HIV-infected adults, adolescents, and children should be screened clinically for TB to identify people who should either be 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 isoniazid preventive therapy (IPT). Pyridoxine is recommended in all HIV-infected persons on INH to mitigate toxicity.
Costs / cost-effectiveness:	There is no information on the costs of this FDC; however the submission 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 USD 200/life-year gained (8). Shrestha et al. used a Markov model to estimate the cost-utility of treating patients with isoniazid for nine months, regardless of PPD status and concluded USD 106/quality adjusted life-year gained in Uganda. These authors found that this treatment approach would produce 30 QALY/100 ALHIV (9). Bell et al. used a Markov model to estimate that six months of isoniazid preventive therapy will save USD 24 per primary or secondary case prevented with IPT (considering medical care and societal costs), will increase life expectancy and quality adjusted life expectancy, and will reduce TB incidence (10). In addition, the submission argued there may be cost savings related to the shipment and storage of the FDC tablets and improved compliance with reduced pill burden for patients.
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 multiple generic suppliers. The INH/B6/CTX FDC is currently under review some national regulatory agencies. At the time of writing, it had not been reviewed by either the U.S. FDA or EMA.
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) in the core list of the EML and EMLc. Listing was recommended in a new sub-section (6.4.2.5) for medicines for the prevention of HIV-related opportunistic infections. The Committee considered that the availability of FDC formulations offer favourable 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 – deletion – 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:	Chris Del Mar, Peter Doshi, Carl Heneghan, Mark Jones, 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 Anti-infective medicines, Other antivirals
Dose form(s) & strengths(s):	Capsule: 30 mg, 45 mg, 75 mg Oral powder: 12 mg/ mL
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	In 2011 oseltamivir was initially listed as a WHO essential medicine soon after the 2009 H1N1 influenza outbreak under what was classified at the time as a public health emergency. Oseltamivir was added with notes to indicate 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 there was limited evidence available on the use of oseltamivir in patients with severe influenza (Table 1). The effect of oseltamivir in reducing the complications of influenza was originally reported in a pooled analysis of 10 manufacturer-sponsored randomized trials of oseltamivir for the treatment of seasonal influenza, not reporting data on mortality (1). The addition of oseltamivir 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 and meta-analyses of 74 studies (2). The few studies providing effects with adjustment for confounders suggested that, in high-risk populations, oral oseltamivir may reduce mortality (3 studies, 681 patients, OR: 0.23, 95% 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, 5.842 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 information from observational studies on severely ill patients is at high risk of bias. In 2013 the Expert Committee reviewed all the evidence available to it and decided to retain oseltamivir in the list. Up until then, no randomised trials of severe or complicated patients had been undertaken and this remains the case today. Further, numerous randomised trials on oseltamivir treatment had never been published. However, in 2014 their results become available through protracted investigations and efforts to retrieve unpublished evidence by independent researchers: a systematic review based on a complete set of clinical study reports of clinical trials of oseltamivir used to support applications for regulatory approval was published in the Cochrane Database of Systematic Reviews (3). The review now includes 53 trials, of which 46 have been formally analysed. In 2016 the Cochrane group published a systematic review of observational studies of oseltamivir in hospitalised patients with 2009/A H1N1 influenza infection (4). The summary data include 30 studies and 11 013 patients for which IPD and survival times were available. Also in 2016 an independent group of experts in complex survival analysis from Germany published a re-analysis of a UK observational study of oseltamivir in hospitalised patients with 2009/A H1N1 influenza infection (5). The data included 1 391 patients with confirmed

pandemic influenza A/H1N1 infection collected during 2009-2010 in the UK. Manufacturer sponsored studies were also published, including an individual patient meta-analysis of observational data in hospitalised patients with 2009/A H1N1 influenza infection (6). This review included 29 234 patients, from 78 centres, for which information on mortality was available. However this large number represents only a fraction of the potentially available data: of 401 centres contacted, only 77 (19%) agreed to contribute data.

As there were no randomised studies of patients with severe influenza, evidence was limited to observational studies primarily of patients hospitalised with 2009/A H1N1 influenza infection to inform on the benefits of oseltamivir for severely ill patients (Table 1).

Table 1. Cumulative evidence for hospitalization and mortality over time in randomized (RCT) and non-randomized (NRS) studies.

Available data*	2010		2017	
	N studies	N patients	N studies	N patients
RCTs – Hospitalization	Subgroup of 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 seasonal influenza viruses, types A, B, and C, which circulate in all parts of the world. Influenza A and B viruses cause outbreaks and epidemics. Only influenza type A viruses are known to have caused pandemics. Influenza type C virus is detected much less frequently and usually causes mild infections.
Illnesses range from mild to severe. Hospitalization and death occur mainly among high-risk groups. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250 000 to 500 000 deaths. In industrialized countries most deaths associated with influenza occur among people age 65 or older (7). Epidemics can result in high levels of worker/school absenteeism and productivity losses. The effects of seasonal influenza epidemics in developing countries are not fully known, but research estimates indicate that about 28.000 to 111.500 children under 5 years of age die from influenza related lower respiratory tract infections in 2008 (8).
Influenza is usually self-limiting in healthy individuals. Treatment of uncomplicated disease in healthy individuals is supportive and includes antipyretics, adequate fluid intake, rest, and staying off work or school until 24 hours after resolution of fever to limit spread to others.
The most effective way to prevent the disease is vaccination.
Antiviral drugs for treating influenza are available in some countries. Ideally, they need to be administered within 48 hours of onset of symptoms. There are 2 classes of such medicines:
1. Inhibitors of the influenza neuraminidase protein (oseltamivir, zanamivir, peramivir and laninamivir which are licensed in several countries).
2. M2 proton channel blockers adamantanes (amantadine and rimantadine), to which virus resistance has been frequently reported, limiting the effectiveness of treatment.
Only oseltamivir is listed as an essential medicine.

Summary of evidence: benefits
(from the application)

Evidence in the application has been complemented with additional evidence integrated by the EML Secretariat.
Benefits associated with oseltamivir have been summarised in five main evidence syntheses. The first systematic review included published and unpublished randomised, placebo-controlled trials and regulatory comments. The review used data from 46 trials (20 oseltamivir and 26 zanamivir studies). The application offered an extract on efficacy from the systematic review abstract results: “In treatment trials on adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% confidence interval 8.4 to 25.1 hours, P<0.001). There was no effect in children with asthma, but there was an effect in otherwise healthy

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	children (mean difference 29 hours, 95% confidence interval 12 to 47 hours, P=0.001). In treatment trials there was no difference in admissions to hospital in adults (risk difference 0.15%, 95% confidence interval −0.91% to 0.78%, P=0.84) and sparse data in children and for prophylaxis. In adult treatment trials, oseltamivir reduced investigator mediated unverified pneumonia (risk difference 1.00%, 0.22% to 1.49%; number needed to treat to benefit (NNTB) 100, 95% confidence interval 67 to 451). The effect was not statistically significant in the five trials that used a more detailed diagnostic form for "pneumonia," and no clinical study reports reported laboratory or diagnostic confirmation of "pneumonia." The effect on unverified pneumonia in children and for prophylaxis was not significant. There was no significant reduction in risk of unverified bronchitis, otitis media, sinusitis, or any complication classified as serious or that led to study withdrawal. 14 of 20 trials prompted participants to self-report all secondary illnesses to an investigator (9)." Evidence from RCTs has been criticised for not being generalizable to the 2009 A/H1N1 influenza virus pandemic, as trials were conducted during seasonal flu as opposed to pandemic flu, which is more severe and associated with frequent complications. However, the expectation of regulatory approval and others is that the effects that these medicines demonstrated in clinical trials might be generalized to other strains of influenza A and B. The systematic review and the application provided data of prophylactic use of oseltamivir. Antiviral chemoprophylaxis is generally not recommended in WHO guidelines (10) nor it is included in the EML for this indication. However, during pandemics WHO guidelines recommend treatment in high risk patients exposed to a patient with influenza. "In prophylaxis trials, oseltamivir reduced symptomatic influenza in participants by 55% (3.05%, 1.83% to 3.88%; NNTB 33, 26 to 55) and households (13.6%, 9.52% to 15.47%; NNTB 7, 6 to 11) based on one study, but there was no significant effect on asymptomatic influenza and no evidence of a reduction in transmission (9)." Since 2012, at least three individual participant data analyses of neuraminidase inhibitors (primarily oseltamivir) potential effect on mortality were published, based on observational data from the 2009 H1N1 experience (i.e. pandemic flu). Two were published by independent groups (4, 5) and found no effect on mortality, whereas the third, published by a group funded by the manufacturer of oseltamivir, did report a protective effect of neuraminidase inhibitors (6). The results of these studies were as follows: The manufacturer funded study of oseltamivir 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 account of the time-dependent nature of exposure to oseltamivir thus possibly introducing immortal time bias (11). Other important biases (i.e. those receiving oseltamivir were younger and more wealthy thus at lower risk) have also been suggested (12). Immortal time bias (a type of time dependent bias) is particularly problematic in cohort studies because it consistently biases the results in favour of the medicine under study by conferring a spurious survival advantage to the treated group. Its magnitude can be easily sufficient to attribute large effects to a non-effective intervention. 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 (HR 1.03, 95% CI: 0.64 to 1.65) (4)." The second independent study, accounting for this time-dependent dynamics of the data, concluded: "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)." Prior to 2014 limited observational evidence used by WHO suggested a possible large effect of oseltamivir on mortality during the pandemic, with an odds ratio of 0.23 (95% CI: 0.13–0.43) based on low quality evidence from three small studies (2). The manufacturer-sponsored study summarised above suggests a much smaller effect on mortality (OR=0.81). The difference was most prominent when small early-published observational studies were compared with subsequent studies. The two recent independent studies suggest oseltamivir has no beneficial effect on mortality in hospitalised patients. These latter results are consistent with the independent review of the entire randomised evidence base of oseltamivir which concluded there is a modest positive effect on the symptoms of influenza but effects on

	more clinically important outcomes such as complications of influenza are unproven.
Summary of evidence: harms (from the application)	The application offered an extract on safety from the systematic review abstract results (9): "Oseltamivir in the treatment of adults increased the risk of nausea (risk difference 3.66%, 0.90% to 7.39%; number needed to treat to harm (NNTH) 28, 95% confidence interval 14 to 112) and vomiting (4.56%, 2.39% to 7.58%; 22, 14 to 42). In treatment of children, oseltamivir induced vomiting (5.34%, 1.75% to 10.29%; 19, 10 to 57)." "In prophylaxis studies, oseltamivir increased the risk of psychiatric adverse events during the combined "on-treatment" and "off-treatment" periods (risk difference 1.06%, 0.07% to 2.76%; NNTH 94, 36 to 1538) and there was a dose-response effect on psychiatric events in two "pivotal" treatment trials of oseltamivir, at 75 mg (standard dose) and 150 mg (high dose) twice daily (P=0.038). In prophylaxis studies, oseltamivir increased the risk of headaches on-treatment (risk difference 3.15%, 0.88% to 5.78%; NNTH 32, 18 to 115), renal events with treatment (0.67%, −0.01% to 2.93%), and nausea while receiving treatment (4.15%, 0.86% to 9.51%; NNTH 25, 11 to 116)." Prior to 2014 it was well known that oseltamivir could lead to nausea and vomiting but published reports of other rarer adverse effects were too few to make any robust conclusions. Independent analysis of the entire randomised evidence base has shown long-term exposure to oseltamivir (as can occur in prophylaxis) can lead to neuro-psychiatric adverse effects as well as renal syndromes.
Additional evidence: (not in the application)	The Secretariat identified an additional individual patient data meta-analysis of all randomised controlled clinical trials comparing oseltamivir with placebo for treatment of seasonal influenza in adults (13). The review was funded from Roche Pharmaceuticals. 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. The clinical relevance of the outcome is doubtful when compared to mortality or hospitalization. Primary analyses have been conducted on the patients identified as influenza-infected by a positive culture from a nasal or throat swab or greater increase from baseline in antibody titre. This is often referred as analysis of efficacy, the extent to which an intervention is beneficial under ideal circumstances. Analyses of benefits were also repeated for the intention-to-treat population, i.e. cases of suspected influenza recruited during local influenza outbreak. In the intention-to-treat infected population, there was a 21% shorter time to alleviation of all symptoms for oseltamivir compared with placebo (time ratio 0·79, 95% CI 0·74–0·85; p<0·0001). In the intention-to-treat 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 h (95% CI −36·2 to −16·0) and −17·8 h (95% CI −27·1 to −9·3), respectively. In the intention-to-treat population, the most clinically relevant outcome – 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 (RR 0·61, 95% CI 0·36–1·03; p=0·066). This result was statistically significant in the intention-to-treat infected population: nine (0·6%) of 1591 participants had to be 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 as compared with 9·9% in patients treated with oseltamivir [risk difference 3·7%, 95% CI 1·8–6·1]) and an increased risk of vomiting (3·3% vs 8·0% [4·7%, 2·7–7·3]).
WHO Guidelines:	WHO Guidelines were issued in 2009, influenza pandemic A(H1N1), under emergency conditions. At that time, available data were limited to few randomised and observational trials. •Recommendation 01: Patients who have severe or progressive clinical illness should be treated with oseltamivir. (Strong recommendation, low quality evidence). •Recommendation 02: In situations where (1) oseltamivir is not available or not possible to use, or (2) 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). •Recommendation 03: Patients not in 'at risk' groups (defined below) who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals. (Weak recommendation, low quality evidence). •Recommendation 04: 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). WHO included also additional recommendations for infection with influenza virus strains other than pandemic (H1N1) 2009 virus (10).
Costs / cost-effectiveness:	Oseltamivir's cost varies from US $10 to 20 for a 5-day course, 10 capsules. Costs might vary depending on the country, 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:	These latter results are consistent with the independent review of the entire randomised evidence base of oseltamivir which concluded there is a positive effect on the symptoms of influenza but effects on more clinically important outcomes such as complications of influenza and mortality reductions are unproven. The potential benefits on symptoms appear to be mitigated by the increase in adverse events. Additional evidence confirmed that there are no benefits to symptomatic patients without influenza virus infection. In routine clinical practice administration of oseltamivir should be primarily driven by rapid diagnostic testing or PCR assays. However during pandemics it will be difficult to test all patients. Since the risks of adverse events will be increased in treated patients, the ratio between benefits (e.g. symptom duration) and harms (e.g. risk of nausea and vomiting) will depend on the proportion of the population with true influenza (i.e. influenza-like illness that is attributable to influenza) and possibly the severity of the disease. If there is a high probability that influenza-like illness is caused by influenza virus infection, oseltamivir can reduce the high rates of illness. During a pandemic, early estimates on the expected burden of disease and severity will predict the central or marginal role of oseltamivir. The Committee noted that the data on the use of oseltamivir in severely ill patients with respiratory complications in epidemics and in pandemics came from observational studies, which are usually undertaken without protocols specifying standardized interventions, outcome assessments and data recording procedures. The Committee also noted that new randomized trials with oseltamivir are underway in different countries but have not yet been completed. The Committee considered the possible need for this medicine in severely ill patients and therefore discussed the potential benefit of retaining oseltamivir on the on the EML and EMLc.
Committee Recommendations:	The Expert Committee noted that oseltamivir treatment has been listed under an emergency public health need. This 2009 H1N1 influenza outbreak no longer exists. The Expert Committee noted that there is additional evidence regarding the efficacy and safety of oseltamivir therapy for influenza in seasonal and pandemic flu. The new evidence decreases the previously estimated effect of oseltamivir on relevant outcomes. However, the Executive Committee recognized that oseltamivir is currently the only listed option for critically ill hospitalised patients and for pandemic influenza preparedness. The Expert Committee therefore recommended oseltamivir to be retained, but moved to the complementary EML and EMLc, for critically ill hospitalised patients. The Committee recommended that the next Expert EML committee flags oseltamivir for deletion unless new information supporting its use in seasonal and pandemic outbreaks is provided. There is a need for completing further independent studies in this regard and for its use in pandemic settings. The Expert Committee noted 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

Tenofovir alafenamide – addition – EML

Tenofovir alafenamide	**ATC Code: J05AF13**
Proposal:	The application requested addition of tenofovir alafenamide (TAF) to the core list of the EML for the treatment of chronic hepatitis B (CHB) infection in adults with compensated liver disease.
Applicant:	Gilead Sciences Inc.
WHO Technical Department:	WHO Global Hepatitis Programme
EML / EMLc	EML
Section:	6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors
Dose form(s) & strengths(s):	Tablet 25 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	This was the first application seeking listing of TAF for chronic hepatitis B. 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.
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 (LMICs). 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 dose-range 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 1,298 HBeAg-negative and HBeAg-positive patients with CHB (4, 5). The primary endpoint in each study was the proportion of patients with HBV DNA < 29 IU/mL at week 48, with a pre-specified non-inferiority margin of 10%. The proportion of patients with ALT normalization at week 48 was another measured outcome. In HBeAg-negative patients, there was no significant difference in the proportion of patients receiving TAF or TDF achieving the primary end point (94% vs 93%, difference 1.8%; 95% 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). For ALT normalization, 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 abovementioned Phase 3 studies indicated that the majority of adverse events associated with TAF were of mild to moderate intensity, with the most common being 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 between treatment groups. With regard to renal adverse events, TAF was associated with smaller increases in serum creatinine from baseline to week 48 compared to TDF. The difference was significant only in the study of HBeAG-positive patients. Decreases in estimated glomerular filtration rate (eGFR) were significantly smaller in the TAF group compared with the TDF group in both studies. TAF was also shown to be associated with significantly smaller changes in proteinuria markers for renal tubular function. With regard to effects on bone, TAF was associated with significantly smaller decreases in hip and spine bone mineral density compared to 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. Pooled analyses of the Phase 3 studies have been undertaken to further investigate bone safety with TAF and have to date only been reported as conference posters and oral presentations. The findings in the pooled analyses were in line with the results from the primary analyses (6-8).
Additional evidence: (not in the application)	Tenofovir alafenamide is a prodrug of tenofovir that has been associated with reduced plasma levels of the parent nucleotide at doses considerably lower than the approved dose of tenofovir disoproxil fumarate (TDF). TDF has been associated with renal toxicity associated with active renal secretion via organic anion transporters (OAT) and higher exposure of renal proximal tubules to tenofovir. TAF has not been demonstrated to interact with renal transporters, nor exhibit OAT-dependent toxicity suggesting potential for an advantage 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 co-infection (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 older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2-11 years (strong recommendation, moderate quality of evidence) • In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART. (Strong recommendation, moderate quality of evidence) • In persons with confirmed or suspected antiviral resistance (k.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 of 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.

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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 (GPRM) reports the median treatment cost per year in 2016 for TDF 300 mg as US$ 32.24.
Availability:	Gilead Sciences Inc. Gilead has licencing agreements with generic drug manufacturers in India, South Africa and China, 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 associated with TAF compred to 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 – addition – EML

Elbasvir + grazoprevir	**ATC Code: J05AX68**
Proposal:	The application requested addition of the fixed-dose combination (FDC) of elbasvir + grazoprevir to the core list of the EML for the treatment of chronic hepatitis C virus (HCV) infection, genotype 1 or 4 in adults.
Applicant:	Dr Andrew Hill, University of Liverpool
WHO Technical Department:	WHO Global Hepatitis Program
EML / EMLc	EML
Section:	6.4.4.2 Medicines for hepatitis C – FIXED-DOSE COMBINATIONS
Dose form(s) & strengths(s):	Tablet: 50 mg + 100 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Neither this 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 HCV indicate that an estimated 115 million persons are HCV-Ab positive of which approximately 80 million are chronically infected (1). The prevalence varies greatly by region and population, with the highest burden, in terms of numbers chronically infected, observed in sub-Saharan Africa and South and East Asia. Data from the Global Burden of Disease study indicates that the number of deaths attributable to HCV has been steadily increasing over the past decades from around 330,000 in 1990 to over 700,000 deaths per year 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 scale-up in accessibility to treatment (3). Scale-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). Data suggests that an increase in screening rates and treatment with highly efficacious regimens will be necessary to curb the increased mortality expected over the coming years (4). 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 or who have developed cirrhosis, renal failure, or are co-infected with HIV remain difficult-to-treat subgroups. 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 scale-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 1,894 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 co-infected with HIV and patients with chronic kidney disease. From the intention to treat analyses of these trials, 1,809 of 1,894 patients achieved a sustained virologic response after 12 weeks of treatment (SVR12

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	95.5%; 95%CI: 94.5% to 96.4%). <u>Genotype 4:</u> 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 co-infected 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% to 97.2%). <u>Special populations:</u> 227 treatment naive patients coinfected with HCV and HIV received elbasvir+grazoprevir for 12 weeks in the C-WORTHY (13) and C-EDGE CO-INFECTED (10) trials. SVR12 was achieved in 95.3% of individuals. The C-SURFER (6) trial 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 94.3% of individuals. No dosage adjustments are recommended for patients with renal impairment (18) Efficacy of elbasvir+grazoprevir was evaluated in 201 users of intravenous drugs using opioid agonist therapy (11). SVR12 was achieved in 91.5% of individuals. Five individuals did not achieve SVR12 due to 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 comparable rate of serious adverse events to other treatment regimens. No deaths attributable to the study drug were observed in the trials. Similar to other direct acting antivirals, 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 due to elevated elbasvir+grazoprevir concentrations and ALT 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 clinically relevant drug-drug interactions with elbasvir+grazoprevir include cyclosporine, 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 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). The same 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 of writing. 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 combination of grazoprevir and elbasvir. The presence of baseline NS5A resistance, which

	occurs in about 12% of patients, led to a marked decrease in SVR compared to those without baseline resistance in genotype 1a-infected patients (69% vs 96%, respectively). This combination has not been considered in these guidelines as it had not received stringent regulatory approval at the time of the Guidelines Development Group meeting
Costs / cost-effectiveness:	The US wholesale acquisition cost (WAC) for a 12-week course of elbasvir+grazoprevir is estimated to be US$54,000. Original WACs for other direct acting antivirals currently included on the EML were significantly higher at US$150,000 (simeprevir plus sofosbuvir), US$94,000 (ledipasvir plus sofosbuvir) and US$147,000 (daclatasvir plus sofosbuvir) (18). In comparison, the cost of a 12-week treatment course of elbasvir+grazoprevir in the United Kingdom is GBP36,500 (22). It is not known if Merck, Sharp & Dohme, as the pharmaceutical manufacturer of elbasvir+grazoprevir have any access strategies in place for facilitating access to this product in low- and middle-income countries.
Availability:	Merck Sharp & Dohme
Other considerations:	The Committee noted that there are other DAA FDCs in regulatory pipelines that 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 DAA combinations, the Committee gave priority to the pan-genotypic combinations and recommended listing of sofosbuvir + velpatasvir in preference to this 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 (FDC) of sofosbuvir + velpatasvir to the core list of the EML for the treatment of chronic hepatitis C virus (HCV) infection, genotypes 1 to 6 in adults.
Applicant:	1. Dr Andres Hill, University of Liverpool 2. Gilead Sciences Inc.
WHO Technical Department:	WHO Global Hepatitis Program
EML / EMLc	EML
Section:	6.4.4.2 Medicines for hepatitis C – FIXED-DOSE COMBINATIONS
Dose form(s) & strengths(s):	Tablet: 400 mg + 100 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	This FDC has not been previously considered by the Expert Committee for addition to the EML. A single-agent formulation of sofosbuvir, and a FDC of sofosbuvir in combination with ledipasvir were among six direct-acting antivirals for treatment of hepatitis C added to the core list of the EML in 2015. Currently, a single-agent formulation of velpatasvir is not marketed or available.
Public health relevance: (burden of disease)	Most recent analyses of the global prevalence of HCV indicate that an estimated 115 million persons are HCV-Ab positive of which approximately 80 million are chronically infected (1). The prevalence varies greatly by region and population, with the highest burden, in terms of numbers chronically infected, observed in sub-Saharan Africa and South and East Asia. Data from the Global Burden of Disease study indicates that the number of deaths attributable to HCV has been steadily increasing over the past decades from around 330,000 in 1990 to over 700,000 deaths per year 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 scale-up in accessibility to treatment (3). Scale-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). Data suggests that an increase in screening rates and treatment with highly efficacious regimens will be necessary to curb the increased mortality expected over the coming years (4). 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 or who have developed cirrhosis, renal failure, or are co-infected with HIV remain difficult-to-treat subgroups. 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 scale-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 sustained virological response after 12 weeks (SVR12) of the Phase 3 studies that have evaluated the efficacy of sofosbuvir+velpatasvir with or without ribavirin for HCV genotypes 1-6 are summarised 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 in 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 summarised in detail in the applications: in Application

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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%.

Geno-type	Trials included	Patient Characteristics	Interventions	SVR12/Total (%)
1	ASTRAL-1, ASTRAL-4, ASTRAL-5	TN & TE, cirrhosis, decompensated cirrhosis, HIV coinfected	SOF+VEL (12-24wks)	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 (12-24wks)	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 (12-24wks)	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 (12-24wks)	128/128 (100.0%) 95%CI: 96.5-100.0%
5	ASTRAL-1	TN & TE	SOF+VEL (12wks)	34/35 (97.1%) 95%CI: 84.2->99.9%
6	ASTRAL-1, ASTRAL-4	TN & TE, cirrhosis, decompensated cirrhosis	SOF+VEL (12wks-24wks)	42/42 (100.0%) 95%CI: 90.0-100.0%
TOTAL	All trials above	All above characteristics included	SOF+VEL±RBV (12-24wks)	1348/1406 (95.9%) 95%CI: 94.7-96.8%*

Abbreviations: TN, treatment-naïve; TE, treatment-experienced; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; PR, pegylated interferon
*Not meta-analysis performed, simple addition of trial results
(Source: Application 1)

Efficacy in special populations:

ASTRAL-5 evaluated the efficacy of sofosbuvir + velpatasvir in 106 patients co-infected 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 tenofovir DF-containing regimens 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%.

Virologic failure and resistance:

Treatment regimens involving sofosbuvir + velpatasvir appear to have a high barrier to viral resistance. Hezode et al (12) evaluated the impact of baseline resistance associated variants (RAVs) on treatment outcome and emergence of RAVs at relapse of patients in a pooled analysis of the ASTRAL 1-4 studies. 16-70% of genotype 1-6 patients were observed to have NS5A RAVs at baseline. There was no observed impact of NS5A RAVs on SVR12 rates in sofosbuvir + velpatasvir-treated patients with genotypes 1, 2, 4, 5, and 6 HCV. 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 summarised in the following tables:

Phase 2 trials

Study Reference	Genotypes	Total No. of Patients	D/C due to AE, n (%)	Serious AE n (%)	Deaths, n (%) (causes)
Gane et al. 2016 (13)	1,3	161	0	3 (2%)	0
Everson et al. 2015 (14)	1,2,3,4,5, 6*	377	1 (<1%)	7 (2%)	1 (<1%)
Pianko et al. 2015 (15)	1,3	321	1 (<1%)	8 (3%)	0
Total	1,2,3	859	2 (<1%)	18 (2%)	1 (<1%)

*Very few patients with genotypes 4,5, and 6 included; efficacy results not available by genotype
Abbreviations: AE, adverse event; D/C, discontinuation
Source: Application 1

Phase 3 trials

Study Reference	Genotypes	Total No. of Patients	D/C due to AE, n (%)	Serious AE n (%)	Deaths, n (%) (causes)
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	1,2,3,4,5,6	1408	13 (<1%)	72 (5%)	12 (<1%)

Abbreviations: AE, adverse event; D/C, discontinuation
Source: Application 1

These data show few discontinuations due to adverse events and a similar rate of serious AEs compared to other regimens. None of the deaths observed were considered to be related to the study drug. The higher rate of AEs and deaths in ASTRAL-4 study is likely to be related to the enrolment of individuals with decompensated cirrhosis.

The most common AEs observed with sofosbuvir + velpatasvir, and observed with similar incidence in placebo-treated patients, were headache, fatigue, nasopharyngitis, and nausea (16).

Compared to placebo-treated patients (ASTRAL-1) and patients treated with ribavirin-containing regimens (ASTRAL-2 and-3), patients treated with sofosbuvir + velpatasvir demonstrated improvements in patient-reported outcome (PRO) scores for health related quality of life measures (17, 18). Improvements were observed within the first 4 weeks of treatment, continued to improve during the course of treatment and after completion.

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 of writing. 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 United States 2016 guidelines for

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	treatment of patients with HCV genotypes 1-6 (11, 20).
Costs / cost-effectiveness:	The US wholesale acquisition cost (WAC) for a 12-week course of sofosbuvir + velpatasvir is estimated to be US$74,670. Original WACs for other direct acting antivirals currently included on the EML were significantly higher at US$150,000 (simeprevir plus sofosbuvir), US$94,000 (ledipasvir plus sofosbuvir) and US$147,000 (daclatasvir plus sofosbuvir).The estimated WAC 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 significant unmet HCV disease burden are designated as "Access countries" to whom only production and related costs are charged. The Gilead suggested government price for 12-weeks supply of sofosbuvir + velpatasvir in Access countries is US$900.
Availability:	Gilead Sciences Inc. This product is currently licensed in Europe, the United States, Canada and Australia. Gilead has licencing agreements with generic drug manufacturers in India, allowing production and sale of generic versions of this medicine in 101 developing countries.
Other considerations:	The Committee noted the potential for drug interactions with coadministration of this product with some 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 (HCV) infection on the basis of a favourable benefit to risk ratio and noting that this is the first pan-genotypic DAA 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 (FDC) formulation of artesunate (A) and pyronaridine tetraphosphate (P) + to the core list of EML and EMLc as an artemisinin combination treatment (ACT) 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:	Shin Poong Pharmaceuticals
WHO Technical Department:	WHO Global Malaria Programme
EML / EMLc	EML and EMLc
Section:	6.5.3.1 (Antimalarial medicines) For curative treatment
Dose form(s) & strengths(s):	Tablet: 60 mg + 180 mg; Granules: 20 mg + 60 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Currently, the FDC 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)	Globally 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. Of the estimated 6.2 million, about 5.9 million (95%) were in children aged under 5 years. By 2015, it was estimated that the number of malaria cases had decreased 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 decreased to 306 000 in 2015 (range: 219 000–421 000). The global burden of mortality is dominated by countries in sub-Saharan Africa. Decreases in case incidence and mortality rates were slowest in countries 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 III clinical trials of artesunate + pyronaridine compared with mefloquine + artesunate (MQ + AS) (2), and artemether+lumefantrine (A+L) (3, 4) in a total of 2,803 children and adults with acute, uncomplicated *P. falciparum* malaria in Africa, South East Asia and India. The primary end point was 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 for the difference in PCR-adjusted APCR was greater than -5% (2, 3) or greater than -10% (4). For the comparison with MQ + AS, results at day 28 showed PCR-adjusted ACPR rates of 99.2% (95% CI: 98.3% to 99.7%) and 97.8% (95% CI: 95.8% to 99,1%). The treatment difference was 1.4% (95%CI: 0.0% to 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 artesunate + pyronaridine 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, artesunate + pyronaridine was also found to be non-inferior to the comparator treatments for the secondary endpoints of PCR-adjusted ACPR at 42 days. New infection or recrudescence rates based on Kaplan-Meier estimates were statistically significantly lower with artesunate + pyronaridine compared with MQ + AS through Day 42 (p=0.049). For the comparison versus A+L, no statistically significant difference was found between groups through Day 28 or Day 42 (2-4). In an integrated analysis of all artesunate + pyronaridine and comparator groups Phase III 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 MQ + AS treatment groups at any time point in the ITT population (5). *P. vivax* studies. One study compared the efficacy and safety of artesunate + pyronaridine compared with chloroquine in subjects with acute, uncomplicated *P. vivax* malaria (6). Results at day 14 showed the crude cure rate for artesunate + pyronaridine versus chloroquine of 99.5% and 100% in the EE population (in 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 II/III artesunate + pyronaridine clinical programme included 3,017 subjects who received at least one dose of artesunate + pyronaridine 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 artesunate + pyronaridine in the individual studies and in the integrated analysis of all Phase II/III 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, transaminase increase (1.6/1.8%) and hypoglycaemia (1.0%). Transient elevations in hepatic transaminase levels were a notable safety finding associated with artesunate + pyronaridine (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 has been shown to be similarly well tolerated on repeat dosing as for first administration with repeat dosing intervals as short as 28 days. Where transient ALT elevations 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) based on the criteria of the Drug Induced Liver Injury Network (12). No cases of liver failure or encephalopathy were observed. There was no evidence of coagulopathy and no evidence of a delayed effect.
Additional evidence: (not in the application)	A systematic review by Bukirwa et al (13) included data for artesunate + pyronaridine from six randomized controlled trials enrolling 3,718 children and adults. In two multicentre trials, enrolling mainly older children and adults from west and south-central Africa, both artesunate + pyronaridine and A+L had fewer than 5% PCR-adjusted treatment failures at 42 days, with no differences between groups (1,472 participants, low quality evidence). Fewer new infections at 28 days were observed in patients given artesunate + pyronaridine (RR 0.60, 95% CI 0.40 to 0.90, 1,720 participants, moderate quality evidence), but no difference was detected at 42 day

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	(1,691 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 artesunate + pyronaridine, and 4% for AS+MQ (RR 1.64, 95% CI 0.89 to 3.00, 1,116 participants, low quality evidence). Fewer new infections at 28 days were observed in patients given artesunate + pyronaridine (RR 0.35, 95% CI 0.17 to 0.73, 1,720 participants, moderate quality evidence), but no differences were detected at 42 days (1,146 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 elevation were four times more frequent with artesunate + pyronaridine than with the other antimalarial treatment (RR 4.17, 95% CI 1.38 to 12.62, four trials, 3523 participants, moderate quality evidence).
WHO Guidelines:	The 2015 WHO *Guidelines for the Treatment of Malaria* do not currently recommend artesunate + pyronaridine for general use (conditional recommendation) (14). The Guidelines Development Group considered the data for artesunate + pyronaridine, (based on the systematic review by Bukirwa et al) were promising, but that a recommendation for general use was not possible at the time. The Group noted: – artesunate + pyronaridine may be as effective as A+L and MQ + AS in adults and older children; – current evidence for young children (less than 5 years) is insufficient to conclude artesunate + pyronaridine is as effective as alternative treatments; – elevations in liver function tests occurred four times more frequently with artesunate + pyronaridine 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 (P+A): 180mg / 60mg; U$0.60 – 2.40 per treatment in different weight band Granule (P+A): 60mg / 20mg; U$0.44 -1.33 per treatment in different body weight Tablet (A+L): U$1.34 – 1.58 per treatment in different body weight. Tablet (AS+AQ): U$0.46 – 0.76 per treatment in different body weight.
Availability:	Shin Poong Pharmaceuticals Artesunate + pyronaridine tablets and granules are included on WHO's list of prequalified medicines following a positive opinion under Article 58 by the EMA. Both the tablets and granules are undergoing national approvals in malaria endemic countries. Some African and Asian countries have already approved the product.
Other considerations:	N/A
Committee Recommendations:	The Expert Committee recommended the inclusion 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 to 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 favourable benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

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Artesunate – addition of 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:	Cipla Limited
WHO Technical Department:	WHO Global Malaria Program
EML / EMLc	EMLc
Section:	6.5.3.1 (Antimalarial medicines) For curative treatment
Dose form(s) & strengths(s):	Rectal dose form: 100 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Artesunate rectal dosage form in 50 mg and 200 mg strengths have been included on the EMLc since 2007. Listing includes the same restriction on use for pre-referral treatment of severe malaria only. This additional strength of 100 mg rectal artesunate can offer better compliance to children in the weight range of 5 to <14kg.
Public health relevance: (burden of disease)	Globally in 2015, there were an estimated 214 new cases of malaria with 438,000 deaths due to the disease. There were an estimated 306,000 malaria deaths in children under 5 years of age in 2015. The vast majority of cases occurred in the African and South East Asian regions (1). Mortality from untreated severe malaria approaches 100%. With prompt treatment and supportive care, mortality falls to 10-20%. The risk for death from severe malaria is greatest in the first 24 hours and in the majority of endemic countries, transit time between referral and presentation at health facilities is 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. Gomes et al. analysed 12,068 patients with suspected malaria who could not be treated with oral medication and who 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 endpoints 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 to placebo (1.9% versus 3.8%, risk ratio (RR) 0.49; 95% CI 0.32 to 0.77; p=0.0013) in the group of patients who did not reach treatment facilities in less than 6 hours. In patients reaching facilities within 6 hours, there was no significant reduction in death (3). Karunajeewa et al. compared the efficacy of artensunate suppositories and intramuscular artemether in paediatric malaria patients aged 1-10 years. Seventy-nine children were randomized to receive a combination of one or two 50 and/or 200 mg thermostable artesunate suppositories to a total dose of 8 to 17 mg/kg or artemether at a dose of 3.2 mg/kg. Compared to the artemether-treated children, those receiving artesunate suppositories had a significantly earlier 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 versus 20.4 hours; p = 0.011) (4). The application also presented the results of a study by Sam-Wobo et al. concerning the utilization, efficacy, and parental perception of rectal suppositories in the management of childhood malaria. Two-hundred sixty-four children were administered rectal artesunate at a

	dose of 5-10mg/kg. After twenty-four 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 (10mg/kg bw) 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 100mg averages US$0.33.
Availability:	Cipla Ltd, India Artesunate 100 mg rectal dose form has been submitted for WHO prequalification.
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 strength 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 (FDC) formulation of dihydroartemisinin (DHA) + piperaquine phosphate (PQP) to the core list of EML and EMLc as an artemisinin combination treatment (ACT) option for the first line treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants.
Applicant:	Mirella Franci, Sigma Tau I.f.r.Spa
WHO Technical Department:	Dr Peter Olumese, Dr Andrea Bosman - WHO Global Malaria Programme.
EML / EMLc	EML and EMLc
Section:	6.5.3.1 (Antimalarial medicines) For curative treatment
Dose form(s) & strengths(s):	Tablet: 20 mg + 160 mg; 40 mg + 320 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Currently, the FDC 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)	Globally 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. Of the estimated 6.2 million, about 5.9 million (95%) were in children aged under 5 years. By 2015, it was estimated that the number of malaria cases had decreased 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 that had 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 South East Asia and in Africa. The Asian trial (2) was a randomised, active-controlled, non-inferiority trial, to demonstrate the non-inferiority of DHA+PQP in terms of efficacy against artesunate+mefloquine (AS+MQ, the standard reference therapy in South East Asia) in 1,150 adult and paediatric patients aged between 6 months and 62 years. The primary efficacy endpoint was the polymerase chain reaction (PCR)-corrected cure rate at day 63. Results at day 63 showed PCR-corrected cure rates for DHA+PQP versus AS+MQ of 87.9% and 86.6% (intention to treat (ITT) population, p=0.544); 97.0% and 95.3% (modified-ITT population, p=0.161) and 98.7% and 97.0% (per protocol (PP) population, p=0.074), demonstrating similar good results in terms of efficacy for both treatments. For all populations studied, the lower limit of the one-sided 97.5% confidence interval of the difference was above the pre-specified non-inferiority margin of -5%, demonstrating DHA+PQP to be non-inferior to AS+MQ. In addition, the analysis of the 63 days of follow up showed that DHA+PQP significantly reduced the risk of new infections with Kaplan-Meier estimates of the proportions of patients with new infections of 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 artemether+lumefantrine (A/L, the standard reference therapy in Africa) in 1,553 paediatric patients aged 6 months to 5 years, weighing at least 5 kg. The primary efficacy endpoint was PCR-corrected cure rate at day 28. Results at day 28 showed PCR-corrected cure rates for DHA+PQP versus A/L of 90.4% and 90.0% (ITT population, p=0.820); 92.7% and 94.8% (m-ITT population, p=0.128) and of 95.7% for both groups in the PP population (p= 0.988). The study demonstrated that both ACTs had

	similar efficacy to cure uncomplicated *P. falciparum* malaria with the lower limit of the one-sided 97.5% CI of the difference 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 with Kaplan-Meier estimates of the proportions of patients with new infections of 13.6% (95% CI: 11.35% to 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 other clinical studies reported in literature, and summarised 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 compared with the AS+MQ group; 69.4% (DHA+PQP) vs. 72.4% (AS+MQ). 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 serious TEAEs (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% (DHA/PQP) vs. 3.2% (AS+MQ) patients. 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 between treatment groups; 79.3% (DHA+PQP) vs. 80.6% (A/L); p=0.550. There were similar serious TEAEs in the DHA+PQP group compared with the A/L group; 1.7% vs. 1.0% (p = 0.249), respectively, as were also the related STEAEs: 1.5% vs. 0.8% (p = 0.332). Mild QTc prolongation was reported as a TEAE in 2.5% DHA/PQP-treated and 2.6% A/L treated patients. No arrhythmias were reported during the study. A study was conducted to further investigate the QTc interval effects of DHA+PQP observed in the phase III studies. The results showed that the prolongation in QTc observed at the end of the treatment with DHA+PQP administered with a high or a low calorie diet is significantly reduced when the drug is administered in fasting conditions with water (11). These findings resulted in modifications to the Summary of Product Characteristics (SmPC), 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 5kg 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 3,428 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) versus 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) recommends DHA+PQP, as an ACT option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide (strong recommendation, high quality evidence). The WHO guidelines recommend using ACTs to treat pregnant women with uncomplicated *P. falciparum* in the second and third trimester. Due to the limited data on the safety of artemisinin-derivatives in early pregnancy (first trimester), quinine + clindamycin is recommended.
Costs / cost-effectiveness:	Ex-factory prices in EU countries for DHA+PQP (40mg+320mg, pack of 12 tablets) range from €28.56 to €41.59. The average ex-factory prices (IMS data) of DHA+PQP products (40 mg+320mg, pack of 9 tabs) commercialized in 12 French East African countries range from €2.74 to €3.42. Median supplier price for artemether+lumefantrine 20 mg+120 mg is reported as US $0.1703

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	per tablet/capsule (treatment course if 24 tablets/capsules for adults). The application claims that the difference in diminishing reinfections by nearly 50% compared to artemether+lumefantrine will yield significant cost effectiveness benefits.
Availability:	Sigma Tau (Italy) On 9 October 2015, the product obtained the WHO prequalification status. DHA+PQP is marketed in some EU, African and Asian markets. In addition, the product has been sold through governmental agencies or no-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 malaria National 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 the favourable benefit to 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 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 favourable benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

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Section 8: ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES

8.2 Cytotoxic and adjuvant medicines

Erlotinib, gefitinib, afatinib, crizotinib – EML - NSCLC

Erlotinib **Gefitinib** **Afatinib** **Crizotinib**	**ATC Code: L01XE03** **ATC Code: L01XE02** **ATC Code: L01XE13** **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 (EGFR). The application also requested addition of the anaplastic lymphoma kinase (ALK-) inhibitor crizotinib to the complementary list of the EML as first-line therapy for the treatment of NSCLC in patients with ALK gene rearrangements.
Applicant:	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) & strengths(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 TKIs, with therapeutic alternatives limited to gefitinib and afatinib. Individual listing for crizotinib.
Background: (if relevant, eg. 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 therefore the use of tyrosine kinase inhibitors as essential medicines for this disease could 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 in 2012 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 rate in 2012 to be ASR of 19.7 per 100 000. Lung cancer had the second highest absolute incidence globally after breast cancer, and in 93 countries was the leading cause of death from malignant disease, accounting for one fifth of the total global burden of disability-adjusted life years from cancer. Non-small cell lung cancer is the most common form of the disease, accounting 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 epidermal growth factor receptor (EGFR) may benefit from treatment with EGFR tyrosine kinase inhibitors (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 failed to receive a targeted therapy previously may be treated with EGFR-TKIs or crizotinib as salvage therapy (10). *The application did not summarise the evidence and conclusions were not supported by a valid review process. For this reason, evidence has been complemented by the Secretariat.* <u>Erlotinib, gefitinib, afatinib</u> 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, totalling 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 to 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 to 1.22). However, for progression-free survival (PFS), erlotinib showed a statistically significant benefit compared with cytotoxic chemotherapy (4 studies, HR 0.30; 95% CI 0.24 to 0.38). One small trial (FASTACT 2) did report statistically significant OS (HR 0.48; 95% CI 0.27 to 0.85) and PFS (HR 0.25; 95% CI 0.16 to 0.39) gains for participants treated with erlotinib plus cytotoxic chemotherapy when compared to cytotoxic chemotherapy alone, while another trial did not show meaningful differences between erlotinib and vinorelbine (OS HR 2.16; 95% CI

	0.58 to 8.10). It was not possible to combine all single estimates of the effect sizes in an overall estimate. Four trials compared gefitinib to platinum-based chemotherapy. Trial results did not show statistical differences for OS (1 trial, gefitinib versus gemcitabine plus cisplatin: HR of 1.04, 95% CI 0.50 to 2.20; gefitinib versus carboplatin and paclitaxel: two trials, HR 0.95, 95% CI 0.77 to 1.18; gefitinib versus docetaxel plus cisplatin: one trial, HR 1.25, 95% CI 0.88 to 1.78). Four studies provide data for progression-free survival. Trials did show statistically significant differences in time before the cancer progresses between gefitinib and platinum-based chemotherapy, and in some cases to a large extent (gefitinib versus gemcitabine plus cisplatin: HR 0.54, 95% CI 0.27 to 1.10; gefitinib versus paclitaxel plus carboplatin: two trials, HR 0.39, 95% CI 0.32 to 0.48; gefitinib versus docetaxel plus cisplatin: one trial, HR 0.49, 95% CI 0.34 to 0.71). When gefitinib was added to platinum-based chemotherapy and compared to platinum-based chemotherapy (2 studies), results were not significantly different either for OS (HR 1.77, 95% CI 0.50 to 6.23) or PFS (HR 0.55, 95% CI 0.19 to 1.60). Afatinib (n = 709) showed a statistically significant PFS benefit when compared with chemotherapy in a pooled analysis of 2 trials (HR 0.42; 95% CI 0.34 to 0.53). Results for OS were immature. Indirect comparisons showed that the three EGFR-TKIs have similar efficacy but they might 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. <u>Crizotinib</u> For patients with ALK gene rearrangements, when compared to pemetrexed or docetaxel, second-line crizotinib has been associated with improvements in PFS (7.7 months in the crizotinib group and 3.0 months in the chemotherapy group, HR 0.49, 95% CI, 0.37 to 0.64). However overall survival showed no significant improvement with crizotinib as compared with chemotherapy (HR, 1.02; 95% CI, 0.68 to 1.54; P=0.54) (14). In first line, when compared to pemetrexed or cisplatin carboplatin, there was a significantly longer PFS (median, 10.9 months vs. 7.0 months; HR 0.45; 95% CI, 0.35 to 0.60), but no significant improvements in OS (median overall survival was not reached in either group; HR, 0.82; 95% CI, 0.54 to 1.26) among patients given crizotinib (15). Data are still immature to derive firm conclusions. Selective cross-over from the control arm to the intervention one might dilute the benefits associated with crizotinib, making inferences about the effectiveness difficult even when the total number of events required for the final analysis of overall survival is reached. Evidence from one observational study (10) showed that crizotinib was associated with improvement in overall survival compared to chemotherapy: 1-year overall survival was 70% (95% CI 50%–83%) for the crizotinib-treated group versus 44% (95% CI 23%–64%) for the crizotinib-naive group; 2-year overall survival was 55% (95% CI 33%–72%) versus 12% (95% CI 2%–30%) (HR 0·36, 95% CI 0·17–0·75). This is a small study and it 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 on a trial, but were subsequently deemed ineligible for the trial. Patient selection and indication biases could therefore have contributed to a systematic imbalance favouring improved survival in the crizotinib group and worse survival in the control group.

Summary of evidence: harms (from the application)	Both EGFR tyrosine kinase inhibitors 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 & 4 adverse events, but their incidence was 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. Although the incidence is small, hepatic failure and hepatorenal syndrome have been reported in patients treated with erlotinib. The common side effects for crizotinib are diarrhea, edema, 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 suggest that there are imminent price adjustments that will make the cost of the three TKIs comparable in the near future. However, data on costs, cost comparisons or cost analyses were not provided. EGFR tyrosine kinase inhibitors and the ALK inhibitor are more expensive than standard chemotherapies. However, as they are oral medicines, they do not require administration effort compared to chemotherapies (e.g. docetaxel). The latter should be administered in a specialized health care unit.
Availability:	No information provided in the application.
Other considerations:	N/A
Committee Recommendations:	In relation to the application, the Expert Committee noted that the presentation of evidence was inadequate. The application did not follow the standard template, with some important dimensions of the evaluation missing or inadequately addressed. Applications in general would benefit from greater focus on the benefits and harms associated with medicines that have to be evaluated. Extensive search of available evidence is preferable compared to selective inclusion of some studies. Data from trials and reviews should be summarised in the application, along with transparent descriptions of the limitations of the evidence. The application should provide the key information to allow evaluation of the relative merits of medicines proposed for the EML, compared 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 that is sufficient to grant to a cancer medicine the status of essential medicine. The Committee considered that EGFR tyrosine kinase inhibitors and the ALK inhibitor may be a valid treatment option for use in patients with NSCLC. 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 PFS and OS 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 EGFR mutations and ALK gene rearrangements will be an important factor requiring consideration by the Working Group in prioritizing cancer therapies for future

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	EML applications. The 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 NSCLC at its next meeting.

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Nilotinib, dasatinib – addition – EML - CML

Nilotinib **Dasatinib**	**ATC Code: L01XE08** **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 leukemia (CML) and intolerance or hematologic resistance to imatinib.
Applicant:	Union for International Cancer Control (UICC)
WHO Technical Department:	Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention
EML / EMLc	EML and EMLc
Section:	8.2 Cytotoxic and adjuvant medicines
Dose form(s) & strengths(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, eg. resubmission, previous EC consideration)	A comprehensive review of CML medicines was done in 2015. Imatinib was added to the EML. For nilotinib and dasatinib the Expert Committee considered the evidence presented in the second-line setting was insufficient to warrant a positive recommendation.
Public health relevance: (burden of disease)	According to GLOBOCAN, worldwide total leukaemia incidence for 2012 was estimated at 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 CML is a rare disease. 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 is 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 the United States, for instance, rates for new CML cases have been stable over the last 20 years, but death rates have dropped significantly, with 5-year relative survival rising from about 30% to 63% (3).

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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 – nilotinib and dasatinib – have been proposed as second therapies due to their potency and activity against mutated forms of BCR–ABL1. 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 hematologic 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 has been studied in imatinib-resistant or intolerant patients with CML in a phase I dose-escalation study (11). The rates of complete hematologic response and major cytogenetic response in the 40 patients with chronic-phase CML were 92 percent and 45 percent, respectively. Efficacy of dasatinib 70 mg twice daily has also been shown in the myeloid or lymphoid blast phase in phase II trials (8, 12). In the study by Cortes et al., after at least 12 months' follow-up, major cytogenetic responses were achieved in 33% and 52% of patients respectively. Twenty-six percent of myeloid blast-phase patients and 46% of lymphoid blast-phase patients achieved a complete cytogenetic response. 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 large benefits similar to 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 in the vast majority of 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 QALY, nilotinib was found to be cost–effective compared with imatinib, while dasatinib was not. No information is 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 testing 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:	In relation to the application, the Expert Committee noted that it did not follow the standard template, and some important dimensions of the evaluation were missing or inadequately addressed. Despite the application's shortcomings, the Expert Committee considered that nilotinib and dasatinib have been demonstrated to be valid treatment options for use in patients with CML 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 Expert Committee recommended nilotinib and dasatinib be included in 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 to grant to a cancer medicine the status of essential medicine.

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Trastuzumab emtansine – addition – EML – breast cancer

Trastuzumab emtansine (T -DM1)	**ATC Code: L01XC14**
Proposal:	The application requested the addition of trastuzumab emtansine (TDM-1) 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:	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) & strengths(s):	Powder for injection: 100 mg; 160 mg in vial
Core / Complementary:	Complementary
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	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 a cytotoxic agent, a maytansine derivative (DM1) (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 HER2 positive breast cancer (2). The trastuzumab part is a humanized anti-HER2 antibody that seeks out cells that overexpress the HER2 receptors. Trastuzumab exhibits anti-tumour activity by inhibiting angiogenesis and recruiting NK cells through antibody- dependent- cell mediated cytotoxicity (3). Additionally, upon binding to the receptor, the antibody moiety 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. Once 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. However once release, the linker, still covalently bonded to DM1, prevents it from crossing the plasma membrane thus, keeping levels in blood plasma initially low. So T-DM1 has important innovative chemical properties: the SMCC keeps the ADC stable in the extracellular environment and once in the cells it 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 with an incidence of 14.9 million in 2013 (6). Over 60% of the global cancer cases occur in Africa, Asia, and Central and South America, and these regions generally experience a higher mortality relative to incidence rates due to higher proportions of late diagnoses, poor prognosis cancer and the scarce impact of clinical care (7) . High-income countries have benefited from screening programs, network of clinical centres exclusively dedicated 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). In 2013, breast cancer incidence reached 1.8 million, where mortality and morbidity are higher in developing countries than in developed countries [8,257.05 thousand

	DALY (95%CI, 7,517.37-8,998.96) for developing countries vs. 4,811.57 thousand DALY (95%CI, 3,838.96- 5,490.48) for developed countries] (6). Breast cancer is a heterogeneous disease whose response can differ based on individual genotype. Up to 25 % of breast cancers are HER2-positive and with at least 450,000 ($1.8X10^6$ * 0.25) women worldwide newly diagnosed with HER2-positive breast cancer in 2013. Over the past three decades, the understanding of the molecular mechanisms and phenotypic expression profiles of cancer has allowed scientist to develop highly targeted and effective systemic treatments (8). The human epidermal growth factor receptor 2 (HER2) is a 185 kDa transmembrane tyrosine kinase receptor encoded by the ERBB2 breast cancer oncogene. Its overexpression leads to constitutive activation MAPK and AKT signalling pathways that results 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 considered 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 one to two 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), still remain elusive but most patients will develop resistance (12-14). Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data). The 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. In fact only 2 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. was retained and supplemented with information from the technology appraisal from NICE (17). Two notable clinical trials (EMILIA, TH3RESA) examining TDM-1 in the treatment experienced advanced stage breast cancer population were central to the application due to their completion and statistical power. <u>Locally advanced and metastatic breast cancer</u> The pivotal EMILIA study (NCT00829166) was a phase III, international open-label, randomised clinical trial comparing T-DM1 (3.6mg/kg every 3 weeks) with lapatinib (1250 mg daily) plus capecitabine [2000mg/m^2] (LC) in women who had unresectable, locally advanced or metastatic HER2- positive breast cancer and who were previously treated with trastuzumab and a taxane (ie: paclitaxel, docetaxel) (18). Between 2009 and December 2011, 991 patients were randomised. Two co-primary outcome measures were progression free survival (PFS) and overall survival (OS) and significant improvement in PFS and OS favoured T-DM1 with less toxicity. T-DM1 patients experience an increase in median OS 30.9 months compared to 25.1 months of LC treated patients [HR 0.68, 95%CI 0.55-0.85, p<0.001]. PFS was assessed by an independent review and found to be significantly improved for T-DM1 at 9.6 months compared to 6.4 months for LC [HR 0.65, 95%CI 0.55-0.77, p<0.001]. Patient reported outcomes (PRO) that evaluate the subjective impact of the treatment on patient quality of life was shown to be superior for T-DM1. PRO was measured with Trial Outcome Index Physical/Functional/Breast (TOI-PFB) subset of the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire and showed a statistically significant delay in predefined symptom worsening secondary endpoints for T-DM1 compared to LC [7.1 months versus 4.6 months; HR 0.796, 95% CI 0.667-0.951; p=0.0121] (19).

In this study, the median daily dose of capecitabine was 1730 mg per square meter which is slightly different from the dose used in other studies combining lapatinib with capecitabine in advanced breast cancer, which used 2000 mg (20).

The second phase, open-label, III RTC, TH3RESA (NCT01419197), aimed to study T-DM1 in more heavily pre-treated metastatic breast cancer patients with previous exposure to lapatinib (21). In this trial, TDM-1 (3.6 mg/Kg IV, every 21 days) was compared to 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 a single-agent chemotherapy. Randomization of 602 patients occurred 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. The 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. However, final OS was presented at the December 2015 San Antonio Breast Cancer Symposium and showed a significant increase in survival with T-DM1 at 22.7 months vs. 15.8 months for TPC [HR 0.68, p=0.0007] (22).

The meta-analysis conducted by Shen et al. included nine eligible studies, three phase I clinical trials, four phase II clinical trials and two phase III clinical trials. The overall hazard ratios for PFS and OS were calculated meta-analysing three (EMILIA (18), TH3RESA (21), BO21976 (23)) and two (EMILIA, TH3RESA,) controlled trials respectively.

The median PFS significantly favoured T-DM1 ranging from a difference in 2.9 months to 5 months with a total hazard ratio of 0.60 [95%CI 0.53, 0.69]. Cumulative OS was associated with an improved survival for T-DM1 taking patients over TPC prescribed patients [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 (24, 25). As part of the review process, the Institute 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 only available for CL, the company conducted a Bayesian network meta-analysis using a fixed-effect model involving 5 clinical trials (EMILIA, CEREBEL, EGF100151, NCT00777101 and GBG26, table X). They found that, compared to 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 to the hazard of tumour progression or death [HR 0.65, 95%CrI 0.35-1.20]. However, the authors report that the CrI "do not rule out the possibility that T-DM1 is less efficacious than comparators".

<u>Comparison with trastuzumab</u>

Trastuzumab is associated with relevant benefits in HER2 positive breast cancer patient: in a systematic review analysing 8 studies, for a total 11,991 patients, the combined HRs for overall survival (OS) and disease-free survival (DFS) significantly favoured the 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 trastuzumab in combination with a taxane, is considered standard of care (i.e. first line) against metastatic breast cancer. The phase 3 randomized controlled clinical trial MARIANNE, not included in the mentioned review, studied untreated HER2+ MBC patients receiving either T-DM1 plus pertuzumab, T-DM1 plus placebo and the combination of trastuzumab plus a taxane (paclitaxel or docetaxel). In an interim analysis, T-DM1 containing therapies were found to have non-inferior PFS to trastuzumab and taxane treatments. However, overall survival curves essentially overlapped, and median overall survival has not been reached in any arm. T-DM1 was better tolerated contributing to a better quality of life secondary endpoints and less adverse events related treatment discontinuation (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 CL]. The most common grade≥ 3 adverse reaction 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 in TPC compared to T-DM1. Grade 3 or worse thrombocytopenia (6.0% vs. 2.7%) was seen in the T-DM1 arm (22). 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 (OR) associated with T-DM1 was for thrombocytopenia at 8.5 OR [95% CI 3.96, 18.22] for all grades and 7.27 OR [95% CI 1.10, 48.11] for grade 3 or greater. Other significant AEs were all grade fatigue at 1.29 OR [95%CI 1.04, 1.59] and all grade increased transaminases at 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). TDM-1 containing regimens were found to be non-inferior (but not superior) to trastuzumab plus taxane in terms of progression free survival in patients with previously untreated HER2 positive metastatic breast cancer (i.e., first-line setting), and with better tolerability. TDM-1 in the first-line treatment setting for metastatic HER-2 positive breast cancer may be a valid treatment option for some patients.
WHO Guidelines:	N/A
Costs / cost-effectiveness:	After having analysed the technology appraisal, NICE concluded that T-DM1 was a clinically effective for treatment for HER2+ unresectable, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, but it ultimately did not find it to be cost effective based on the price that Roche was offering at the time (25).
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 previously received trastuzumab and a taxane, separately or in combination in: EU (EMA) US (FDA) Australia (TGA) Japan (PMDA) There are currently no biosimilars of T-DM1 on the market. However, in November 2016, 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[3]) . Roche's Herceptin (trastuzumab), was approved by the US Food and Drug Administration (FDA) in September 1998 and by the European Medicines Agency (EMA) in August 2000. Currently there are 3 biosimilar versions of trastuzumab that are commercially available in India and Iran for the treatment of breast cancer, plus a fourth in Russia. There are at least 4 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 approved by the Ministry of Health of the Russian Federation. 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.

[3] http://www.who.int/selection_medicines/committees/expert/21/applications/s8_trastuzumab_emtansine_attach1.pdf?ua=1

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Other considerations:	N/A
Committee Recommendations:	The Expert Committee acknowledged the significant public health burden of breast cancer, afflicting an increasing number of people in all countries, irrespective of income. In addition to TDM-1, the Expert Committee noted the availability of other innovative medicines for this condition (e.g. pertuzumab), and other medicines mentioned in this and previous applications (e.g. lapatinib). These have never been proposed for evaluation for inclusion on the EML. These medicines should be compared to the standard of care, and evaluated as potential essential medicines. The final comprehensive listing 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 TDM-1, the Committee nevertheless recommended that trastuzumab emtansine should not be added to the EML at this time, but should be considered as part of a comprehensive review encompassing additional medicines (e.g. pertuzumab, lapatinib, bevacizumab) at its next meeting. 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, to grant to a cancer medicine the status of essential medicine, taking into consideration various lines of therapy.

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Zoledronic acid – addition – EML – cancer bone metastases

Zoledronic acid	**ATC Code: M05BA08**
Proposal:	The application requested addition of bisphosphonates to the complementary list of the EML as a therapy for the treatment of patients with cancer and bone metastases. The application proposes 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:	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) & strengths(s):	Concentrate 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, eg. 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: 65-75% of patients with advanced prostate cancer and 70% of patients who die of breast cancer will develop bone metastases. 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 GI 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 anti-cancer treatments and no bisphosphonates, SREs occur in 46 to 64% of patients in two years (depending on the underlying malignancy), contributing importantly to the significant overall morbidity of advanced cancer (3-5).

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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 patients with breast cancer experiencing an SRE, extend the time to first and subsequent SREs and prevent around one third of all skeletal morbidity (4, 5, 13, 15). Zoledronic acid is likely to be the most effective agent (16-18) with a 41% reduction in the overall risk of SREs when compared to placebo (19). Placebo controlled trials have also shown benefits for oral clodronate (20-22), intravenous (23, 24) and oral ibandronate (24, 25) and pamidronate (3, 13, 15) although to a lesser extent when compared to 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 intravenous ibandronate has similar efficacy to palliative radiotherapy for the acute relief of bone pain (11). In this disease setting, zoledronic acid decreased 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 SRE by 36% and improved pain scores (4). Similarly, in non-breast and non-prostate solid tumours (50% NSCLC and 50% miscellaneous other solid tumours), zoledronic acid increased the median time to the first event (230 days vs 163 days) and decreased 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)	There are several risks associated with treatment with bisphosphonates that require monitoring (8, 35). Intravenous bisphosphonates are commonly associated with the acute phase response (fever and flu-like symptoms), 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 intravenous bisphosphonate therapy (40, 41); the risk may be less with daily oral agents or administration of intravenous treatment on a 3 monthly schedule (42). It is recommended that patients have a dental exam and preventive dental work (such as tooth extraction) performed prior to administration of bisphosphonate therapy and 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, though this should be individualized based on 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

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	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:	The MSF Drug Price Indicator Guide 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 United States.
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 (45, 46). Administration of zoledronic acid every 12 weeks may be as effective as the approved schedule of every 4 weeks (47-49).
Committee Recommendations:	In relation to the application, the Expert Committee noted that it did not follow the standard template, and some important dimensions of the evaluation were missing or inadequately addressed. Despite the application's shortcomings, the Expert Committee considered that zoledronic acid has been demonstrated to be a valid treatment option for use in patients with malignancy related bone disease. Based on the positive evaluation, the Expert 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 (addition) – EML – prostate cancer

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:	Knowledge Ecology International (KEI)
WHO Technical Department:	WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention
EML / EMLc	EML
Section:	8.2 Cytotoxic and adjuvant medicines
Dose form(s) & strengths(s):	Capsule: 40 mg
Core / Complementary:	Complementary
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Enzalutamide was not included in the review of cancer medicines considered by the Expert Committee in 2015. Following this review, bicalutamide was added to the EML with a square box as representative of the pharmacological class of 'anti-androgens'. Despite enzalutamide being classified by the Anatomical Therapeutic Chemical (ATC) classification system as an anti-androgen and grouped with bicalutamide and similar agents, the mechanism of action of enzalutamide differs from the other anti-androgens. Enzalutamide should not be considered as an alternative to bicalutamide under the square box listing. Bicalutamide is a non-steroidal, first-generation oral anti-androgen and is approved for use in conjunction with LHRH analogues in men with hormone-treatment-naive prostate cancer. Bicalutamide has partial affinity for the androgen receptor and drug resistance can be easily developed. Enzalutamide is a second generation anti-androgen, with higher affinity to androgen receptor, resulting in modifying several steps in the androgen receptor signalling pathway, and inhibiting cancer growth (1).
Public health relevance: (burden of disease)	Prostate cancer is one of the most common cancers. In 2012, approximately 1.1million men were diagnosed with prostate cancer, with 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 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. Although the majority of 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 signaling by preventing the ligand from binding to the AR, and downstream intra-cellular events, interfering with crucial elements that contribute to cancer progression (4). Enzalutamide has a half-life of 5.8 days and is metabolized by CYP2C8 and CYP3A4 and the drug steady state is reached in 28 days (5). When patients are diagnosed with prostate cancer, if they are treated early and tumors are localized, the prognosis is often favorable. 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 with a greater disease burden. Access to second generation therapies such as enzalutamide becomes a potential option to prolong life of the patient eventually. 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. However, meta-analyses were found comparing enzalutamide, abiraterone (although not head-to-head) and other therapies in various treatment exposure settings. Key RTCs have been summarised, along with a meta-analysis comparing enzalutamide with another second generation inhibitor. Summary of available data The AFFIRM clinical trial (NCT00974311) was a phase III randomized, double-blind, placebo-controlled, multicenter trial to study the efficacy and safety of enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC) who had previously taken docetaxel (6). 1,199 adult males, ranging from 41 to 92 years, were randomized in a 2:1 ratio, where 800 participants received a dose of 160mg of enzalutamide once a day, 399 participants received a placebo, and all continued on androgen deprivation therapy. OS was found to be 18.4 months for enzalutamide and 13.6 months for the control arm [HR 0.63; 95% CI 0.53–0.75]. PFS was 8.3 for enzalutamide versus 2.9 for the placebo [HR 0.40; 95% 0.35–0.47]. 54% of patients in the treatment arm experienced 50% or greater decrease in PSA levels compared to only 2% in the control arm. The trial was stopped at the interim analysis having demonstrated an improved OS. The result from the AFFIRM formed the bases for the initial FDA approval. PREVAIL investigated enzalutamide in first line setting in mCRPC who had not yet received chemotherapy(7) . This pivotal phase III, placebo controlled clinical trial, enrolled 1717 patients that were randomized 1:1. As with AFFIRM, PREVAIL was stopped early for benefit after interim results were collected. Less deaths were reported in the treatment arm at 28% vs 35% for placebo [HR: 0.71, 95% CI: [0.60–0.84]]. The median overall survival 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) progression-free survival 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 to 0.23). The benefit of enzalutamide was shown with respect to all secondary end points. Based in the results from this trials, the FDA approved enzalutamide for used in first-line therapy for mCRPC. Two studies compared enzalutamide to 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 to 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 to bicalutamide (9). Patients in the enzalutamide group had significantly improved median progression-free survival (HR 0·44 [95% CI 0·34–0·57]): median PFS 15.7 months with enzalutamide and 5.8 months with bicalutamide.

Summary of evidence: harms (from the application)	Overall, enzalutamide seems to be well tolerated. In the AFFIRM trial there were few adverse events (AE) of grade 3 or above (45.3%, versus 53.1% in the placebo group) (6). It was noted that the rates of adverse events were similar in the two groups despite the period of observation for the enzalutamide group was more than twice that for the placebo group. Grade ≥3 events relating to fatigue (6% vs7%), diarrhea (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, as compared with 4.2 months in the placebo group. The PREVAIL data showed similar harm data: there were few adverse events (AE) of grade 3 or above (43%, versus 37% in the placebo group) (7). The median time until 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 cardiac severe 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 endpoint. 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, having a US wholesale price of about $10,549 for a supply of 120 capsules (10). Four 40 mg capsules of enzalutamide are administered orally daily. Enzalutamide could be marginally cost-effective compared with abiraterone or with best supportive care. ICERs vary depending on countries. In the United Kingdom, ICERs range from about US$ 19,000 per QALY gained for enzalutamide when compared to 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 to compared with supportive care exceeds US$ 100.000 (12, 13). These studies are not particularly useful when considering if enzalutamide would be cost effective 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 $1 per day for a 4x40mg dose.
Availability:	Enzalutamide has several advantages over the other treatments used to treat CRPC (e.g. docetaxel requires I.V. administration; use of radium-223 and radiopharmaceuticals is often confined to tertiary care level facilities). Enzalutamide and abiraterone acetate are the only daily oral tablets. Enzalutamide's pill burden is lighter 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, afflicting an increasing number of people in all countries. The Expert 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 alternative options potentially associated with

	survival gains should be considered a priority. A comprehensive evaluation of prostate cancer treatment options, will support countries to better understand 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, to grant to a cancer medicine the status of essential medicine. While acknowledging the good quality of the application in presenting evidence to support the listing enzalutamide, the Committee nevertheless recommended that enzalutamide should not be added to the EML at this time, but should be considered as part of a comprehensive review encompassing additional medicines (e.g. abiraterone) at its next meeting.

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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 Darbepoetin alfa Methoxy polyethylene glycol-epoetin beta	**ATC Code:** B03XA01 B03XA02 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:	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 non-communicable diseases
EML / EMLc	EML and EMLc
Section:	10. Medicines affecting the blood; 10.1 Antianaemia medicines
Dose form(s) & strengths(s):	EML: ☐ 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 epoietin alfa, beta and theta, darbepoietin alfa, methoxy polyethylene glycol-epoetin beta and their respective biosimilars. EMLc: ☐ 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 epoietin alfa and beta, darbepoietin alfa and their respective biosimilars. ESAs are available as a solution for intravenous or subcutaneous injection. Table 1 reports the dosing for treating anemia of chronic kidney disease in adults and pediatric patients with end-stage renal disease undergoing dialysis. Correction phase refers to the doses needed to reach a target hemoglobin (Hb) level of 11-12 g/dL. Maintenance phase refers to the doses to keep the target Hb level stable (1, 2) (KDIGO 2012, KDIGO 2013). Table 1. Adapted from Dynamed Plus 2016 (3). **Medicine - Adult dosing** Epoetin alfa and biosimilars — 50 to 100 units/kg - three times per week

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Epoetin beta*	Correction phase: 40 units/kg - three times per week Maintenance phase: half the previous dose
Epoetin theta*	Correction phase: 20 units/kg SC or 40 units/kg IV - three times per week Maintenance phase: 25% dose adjustments to maintain Hb target (10 - 12 g/dL)
Darbepoetin alfa	*Epoetin alfa naive patients* Correction phase: 0.45 mcg/kg IV (preferred route) or SC once weekly or 0.75 mcg/kg IV or SC once every two weeks as needed *Switch from epoetin alfa* Dose based on the weekly epoetin alfa dose (maintain the same route of administration) Refer to labeling information for conversion dosages
Methoxy polyethylene glycol-epoetin beta	*ESA naïve patients* Correction phase: 0.6 mcg/kg as a single IV (preferred route) or SC injection once every two weeks Maintenance phase: double the dose used in the initial phase IV (preferred route) or SC once monthly Refer to labeling information for conversion dosages
Pediatric dosing	
Epoetin alfa and biosimilars	50 units/kg - three times per week
Epoetin beta*	Correction phase: 40 units/kg - three times per week Maintenance phase: half the previous dose
Epoetin theta*	Not established
Darbepoetin alfa	*Epoetin alfa naive patients* Initial: 0.45 mcg/kg IV (recommended) or SC once weekly *Switch from epoetin alfa* Dose based on the weekly epoetin alfa dose (maintain the same route of administration)
Methoxy polyethylene glycol-epoetin beta	Not established

*not licensed in the United States.
SC: subcutaneous; IV: intravenous; target Hb levels 11-12 g/dL in adults and 12 g/dL in pediatric patients (KDIGO 2013).

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

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	• 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, eg. resubmission, previous EC consideration)	Currently, the antianaemia medicines 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/1.73 m^2) for three or more months, irrespective of the cause. The prognosis of chronic kidney disease and the need for renal replacement therapy (either dialysis or kidney transplant) depend on the following variables: 1) cause of chronic kidney disease; 2) GFR category; 3) albuminuria category; 4) other risk factors and comorbid conditions (e.g. hypertension, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease) (2). End-stage renal disease refers to people with stage 5 chronic kidney disease undergoing dialysis, and recipients of kidney transplant. The KDIGO 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/1.73 m^2. 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 mainly due to erythropoietin deficiency which itself is principally caused 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. Renal anaemia can thus be regarded as a hormone deficiency state. According to the World Health Organization (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 nonpregnant 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 occurred 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, though 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). Anemia is one of the several complications of chronic kidney disease. Its prevalence (from any

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	cause) in patients with renal failure is about 15% in the United States (10). In chronic kidney diseases end stages, about 1 in 2 patients is severely anaemic. The main impact of anemia on organ function is reduced oxygen delivery to tissues, leading to debilitating symptoms such as fatigue, exercise intolerance, impaired cognitive function, sleep disorder, altered hemostasis, and depressed immune function. Anemia in patients with chronic kidney disease is associated with decreases in cardiac and renal functions, quality of life, and poses a significant clinical and economic burden on healthcare systems. Anemia is also associated with a high prevalence of cardiovascular diseases in renal patients, and their 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 impairment in cognition (12).
Summary of evidence: benefits (from the application)	The application summarizes the evidence on the effectiveness and safety of ESAs, including branded medicinal products and biosimilars, for the treatment of anemia 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 pharmacoeconomics analyses comparing erythropoietins (epoetin alfa, beta, theta, zeta), darbepoetin alfa, and CERA to: 1) no intervention, placebo, standard care; 2) other ESAs; 3) other interventions (e.g., iron supplementation, androgen); 4) different dosages and administration schedules of the same ESA; and 5) 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 section Costs), one RCT published in 2015 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 the network meta-analysis published in 2014 by Palmer et al., that summarizes 56 studies for a total of 15,596 participants (17). This review compared the efficacy and safety of different ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta, and biosimilar ESAs, against each other, placebo, or no treatment). <u>Epoetin alfa and beta versus placebo/no treatment/standard care (Summary of Findings 1)</u> The evidence collected 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. Epoetin alfa and beta do not appear to affect the risk of vascular access thrombosis but increase the risk of hypertension. The quality of evidence was judged as 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 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. <u>Darbepoetin versus other ESAs (epoetin alfa and beta, CERA) (Summary of Findings 2)</u> 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 collected suggests that darbepoetin reduces the risk of requiring blood transfusions compared to epoetin alfa but not to CERA. The quality of evidence was judged 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. Noteworthy, the benefit of darbepoetin in reducing blood transfusions was supported by high-quality evidence. These results were largely driven by industry-sponsored trials.

CERA versus epoetin alfa and beta (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 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 largely driven by industry-sponsored trials.

Originators (epoetin alfa) versus biosimilars (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 as low because of the unclear risk of selection bias and the imprecision of the estimates, with the exception of the findings on hypertension supported by evidence of moderate quality due to unclear risk of selection bias only. 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 nondialysis population, four in the dialysis population, and one in a combined sample. In all, the review showed that higher versus lower Hb targets resulted in only small and, in many cases, non-significant 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 were 1.65 (95% 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 including 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 (Summary of Findings 4 b). 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 regarding the interchangeability and switching from originators to biosimilars. These concerns were addressed in a comprehensive systematic review by the Swedish Council of Health Technology Assessment 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. Fourteen 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 could demonstrate immunological and clinical consequences when switching between products.

Children

Although children differ substantially from adults, providers caring for adult and pediatric patients with chronic kidney disease largely share the same concerns regarding the diagnosis and management of anemia. As generally the evidence in children is scarce and of low quality, it is unavoidable to generalize from evidence in adults. The review by Palmer et al. of 2010 identified two RCTs in children with end-stage renal disease (26, 27) and one additional study was included in the review by Palmer et al. 2014 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 erythropoietin alfa and beta, with some preliminary data on darbepoetin. In children with chronic kidney disease stages 4 and 5, darbepoetin alfa compared to epoetin 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 (NAPRTCS) 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% confidence interval [CI], 1.03 to 2.26). Patients with more severe anemia also had an increased risk of hospitalization. In a multicenter single-arm interventional trial evaluating 22 children with chronic kidney disease (4 months to 16 years) treatment of anemia 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 versus 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. Therefore, the lowest effective dose is recommended (30). All proprietary ESAs raised the odds of hypertension compared to 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 anemia, with or without cytopenia, associated with neutralizing antibodies to erythropoietin, were reported in Europe and in the United States, primarily in patients with chronic kidney disease given the medicine by subcutaneous injection. This was probably due to the interaction of stabilizing agent and part of the the pre-filled syringes. Despite modifications in the prefilled 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 35.8/100000 patient-years (95% CI 7.4 to 104.7) for epoetin alpha, 14.0/100 000 patient-years (95% CI 1.7 to 50.6) for 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 subcutaneous 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 three 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,

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	up to three times per week. This led to development of ESA agents with longer half-life (i.e. darbepoetin alfa, CERA), hence lower dosing frequency. The dosing schedules of once-weekly or once every two weeks with darbepoetin and monthly dosing with CERA potentially offer many advantages to both patients and caregivers (35). However, the impact of this 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 one to four-week intervals were non-inferior to ESA given one to three times/week in terms of achieving Hb targets, without any significant differences in adverse events in hemodialysis 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 below. Studies that evaluated different Hb targets showed that reaching 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 hemodialysis patients were lower than 9 g/dL, providing epoetins in order to reach Hb 10 to 11g/dL was less costly and more effective than higher or lower Hb levels. Reported cost/QALY ratios ranged from US dollars 931 to 677,749/QALY across five studies comparing ESAs to 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 hemodialysis center ranged from 288:1 to 400:1 and the average annual per-patient saving ranged from US dollars 2140 to 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 to other ESAs. Review findings were contradictory, some demonstrating an increase of costs associated with CERA and others a cost reduction (40). It is expected that the introduction of biosimilars of epoetin has an impact on prices and drug market. Price differences between biosimilars and originators has been broadly estimated 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, UK, Italy, Spain, Sweden, Poland and Romania) was provided by Haustein et al. in a report supported by Sandoz Pharmaceuticals (42). On the basis of the data provided by IMS Health, this paper evaluated how biosimilars can help reducing healthcare expenditure over the long term, through the increased use of biosimilars rather than originators. The estimated cumulative saving for biosimilar epoietins was EUR 9.4 to 11.2 billion, subject to the expected market share trend and scenarios. The expected savings amount to 21.4 to 25.5% of the EUR 43.8 billion estimated 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 the overall biosimilar sales are still a relatively small segment of the European market, but have a strong annual growth. Considering epoetins, the highest uptake was reported in Germany, Greece and Sweden (43).
Availability:	ESAs are licensed globally with the following indication: "Treatment of symptomatic anemia 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 the US in 2024 (42). Darbepoetin alfa 'similar biologic' drugs (Actorise, Cresp, Darbatitor) are available in India (42). To be licensed in the countries with stringent regulatory agencies as those of the European Union and United States, 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 for providing a comprehensive data package have often been claimed as putting an unnecessary burden (and cost) on the development and licensing, thus leading to delay in the access to biosimilars. On the other hand, these criteria are meant to provide a sufficient level of evidence and extrapolation to reduce patients and health care professionals' concerns about the use of biosimilars. Still, the adoption of such criteria is 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 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) due to 19 reports of anaphylaxis after the first dose (including three deaths) in patients receiving dialysis (48).
Committee Recommendations:	The Expert Committee noted that erythropoiesis-stimulating agents have been demonstrated 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 demonstrated 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 epoietin alfa, beta and theta, darbepoietin alfa, methoxy polyethylene glycol-epoetin beta and their respective biosimilars (EML) and epoietin alfa, beta and theta, darbepoietin alfa, and their respective biosimilars (EMLc).

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Summary of findings 1: Epoetin alfa or beta compared to placebo/no treatment/standard care for the 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* (95% CI)		Relative effect (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 to 87)	**OR 0.78** (0.41 to 1.48)	774 (4 RCTs)	⊕⊕◯◯ LOW [a,b]	
Major cardiovascular events	19 per 1000	**6 per 1000** (0 to 136)	**OR 0.33** (0.01 to 8.21)	106 (1 RCT)	⊕⊕◯◯ LOW [a,b]	
Blood transfusions	437 per 1000	**30 per 1000** (8 to 104)	**OR 0.04** (0.01 to 0.15)	329 (3 RCTs)	⊕⊕⊕⊕ HIGH [a,c]	
Vascular access thrombosis	58 per 1000	**121 per 1000** (24 to 443)	**OR 2.23** (0.39 to 12.88)	217 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	
Hypertension	83 per 1000	**245 per 1000** (171 to 338)	**OR 3.59** (2.29 to 5.64)	843 (5 RCTs)	⊕⊕⊕⊕ HIGH [a,c]	
Final/Change in Hb level	The mean final/change in Hb level was **0**	The mean final/change in Hb level in the intervention group was 0 (0 to 0)	-	(0 studies)	-	

***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). **CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

a. unclear risk of selection bias
b. small number of events, 95% CI includes 1
c. large magnitude of effect

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Summary of findings 2: Darbepoetin compared to other ESAs for the 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* (95% CI)		Relative effect (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 to 1.80)	2639 (12 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	
All-cause mortality - Darbepoetin vs CERA	68 per 1000	**65 per 1000** (38 to 108)	**OR 0.95** (0.55 to 1.67)	798 (2 RCTs)	⊕⊕⊕◯ MODERATE [b]	
Major cardiovascular events - Darbepoetin vs Epoetin alfa	37 per 1000	**20 per 1000** (9 to 46)	**OR 0.53** (0.23 to 1.24)	1023 (2 RCTs)	⊕◯◯◯ VERY LOW [a,b,d]	
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 to 0.64)	1269 (3 RCTs)	⊕⊕⊕⊕ HIGH [a,e]	
Blood transfusions - Darbepoetin vs CERA	135 per 1000	**128 per 1000** (88 to 180)	**OR 0.94** (0.62 to 1.41)	802 (2 RCTs)	⊕⊕⊕◯ MODERATE [b]	
Vascular access thrombosis - Darbepoetin vs Epoetin alfa or beta	112 per 1000	**109 per 1000** (78 to 150)	**OR 0.97** (0.67 to 1.40)	1432 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,d]	
Vascular access thrombosis - Darbepoetin vs CERA	90 per 1000	**70 per 1000** (37 to 127)	**OR 0.76** (0.39 to 1.47)	489 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	
Hypertension - Darbepoetin vs Epoetin alfa or beta	199 per 1000	**205 per 1000** (166 to 249)	**OR 1.04** (0.80 to 1.34)	1591 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,d]	

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Hypertension - Darbepoetin vs CERA	123 per 1000	**95 per 1000** (63 to 141)	**OR 0.75** (0.48 to 1.17)	798 (2 RCTs)	⊕⊕⊕◯ MODERATE [b]
Final/change in Hb level - Darbepoetin vs Epoetin alfa	The mean final/change in Hb level - Darbepoetin vs Epoetin alfa was **0**	The 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 [a,f]
Final/change in Hb level - Darbepoetin vs CERA	The mean final/change in Hb level - Darbepoetin vs CERA was **0**	The 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 [g]

*__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).
CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

a. unclear risk of selection bias
b. small number of events, 95% CI includes 1
c. high risk of selective reporting bias (8 out of 12 studies)
d. all studies at high risk of selective reporting bias
e. large magnitude of effect
f. 95% CI includes zero
g. sample size less than 400

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Summary of findings 3: CERA compared to other ESAs for the anemia of end-stage kidney disease in dialysis patients

Patient or population: dialysis patients with anemia of end-stage kidney disease
Intervention: methoxy polyethylene glycol-epoetin beta (CERA)
Comparison: other ESAs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (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 EPO	62 per 1000	**64 per 1000** (41 to 97)	**OR 1.03** (0.65 to 1.62)	1341 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	
All-cause mortality - CERA every 4 weeks vs EPO	59 per 1000	**68 per 1000** (42 to 107)	**OR 1.16** (0.70 to 1.92)	1108 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,d]	
Blood transfusions - CERA every 2 weeks vs epoetins	90 per 1000	**83 per 1000** (58 to 118)	**OR 0.91** (0.62 to 1.35)	1341 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	
Blood transfusions - CERA every 4 weeks vs epoetins	87 per 1000	**87 per 1000** (55 to 134)	**OR 1.01** (0.62 to 1.64)	827 (2 RCTs)	⊕⊕◯◯ LOW [b,e]	
Vascular access thrombosis - CERA vs epoetin beta	87 per 1000	**51 per 1000** (15 to 164)	**OR 0.57** (0.16 to 2.06)	181 (1 RCT)	⊕⊕◯◯ LOW [a,b]	
Hypertension - CERA vs epoetin beta	239 per 1000	**185 per 1000** (91 to 337)	**OR 0.72** (0.32 to 1.62)	181 (1 RCT)	⊕⊕◯◯ LOW [a,f]	
Final/change in Hb level - CERA every 2 weeks vs epoetins	The mean final/change in Hb level - CERA every 2 weeks vs EPO was **0**	The 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 [a,c,g]	
Final/change in Hb level - CERA every 4 weeks vs EPO	The mean final/change in Hb level - CERA every 4 weeks vs EPO was **0**	The 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 [a,e,g]	

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*__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).
CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

a. unclear risk of selection bias
b. small number of events, 95% CI includes 1
c. three out of four studies reported ITT data only graphically
d. two out of three studies reported ITT data only graphically
e. all studies reported ITT data only graphically
f. sample size less than 400, 95% CI includes 1
g. 95% CI includes zero

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Summary of findings 4: Biosimilars compared to epoetin alfa for the anemia of end-stage kidney disease in dialysis patients

Patient or population: dialysis patients with anemia of end-stage kidney disease
Intervention: biosimilars
Comparison: epoetin alfa

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with epoetin alfa	**Risk with biosimilars**				
All-cause mortality	37 per 1000	**48 per 1000** (31 to 74)	**OR 1.32** (0.83 to 2.09)	1883 (6 RCTs)	⊕⊕◯◯ LOW [a,b]	
Major cardiovascular events	69 per 1000	**80 per 1000** (48 to 132)	**OR 1.17** (0.67 to 2.04)	718 (3 RCTs)	⊕⊕◯◯ LOW [a,b]	
Blood transfusions	29 per 1000	**40 per 1000** (24 to 66)	**OR 1.41** (0.83 to 2.38)	1823 (3 RCTs)	⊕⊕◯◯ LOW [a,b]	
Hypertension	69 per 1000	**39 per 1000** (23 to 66)	**OR 0.55** (0.32 to 0.95)	1464 (4 RCTs)	⊕⊕⊕◯ MODERATE [a]	
Vascular access thrombosis	35 per 1000	**24 per 1000** (10 to 58)	**OR 0.69** (0.28 to 1.70)	823 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	
Final/Change in Hb level	The mean final/change in Hb level was **0**	The mean final/change in Hb level in the intervention group was 0	-	(0 studies)	-	Outcome not reported in the analysed reviews

***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).
CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

a. unclear risk of selection bias
b. small number of events, 95% CI includes 1

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Section 12: CARDIOVASCULAR MEDICINES

12.3 Antihypertensive medicines

Lisinopril + hydrochlorothiazide – addition – EML

Lisinopril + hydrochlorothiazide	**ATC Code: C09BA03**
Proposal:	The application proposed the addition of a fixed-dose combination (FDC) formulation of lisinopril and hydrochlorothiazide (HCTZ) to the core list of the EML for treatment of hypertension in patients not adequately controlled with monotherapy. It is recommended that patients should be first stabilized on the component medicines at the same dosage before initiating treatment with the corresponding FDC. Listing was requested with a square box to represent the pharmacological classes of angiotensin converting enzyme (ACE) inhibitors and thiazide diuretics.
Applicant:	Abdul Salam and colleagues, The George Institute for Global Health, University of Sydney
WHO Technical Department:	Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention
EML / EMLc	EML
Section:	12.3 Antihypertensive medicines
Dose form(s) & strengths(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, eg. resubmission, previous EC consideration)	The pharmacological class of ACE inhibitors is represented on the EML with a square box listing for enalapril. This listing would capture lisinopril. Hydrochlorothiazide 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). Globally, in 2015, there were over 1 billion adults with raised blood pressure, compared to almost 600 million in 1975. The majority of the 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 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 applicant identified seven randomized controlled trials 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 to 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 randomized controlled trials involving 35,208 patients (14-24). For all studies combined, the review found combination antihypertensive therapy to significantly reduce the risk of cardiovascular outcomes. The risks were reduced to a greater extent when only trials demonstrating a reduction in systolic blood pressure of greater than 6 mmHg were considered. Results are reproduced in the table below:

Table 4 (page 8 of the application): Effects of combination therapy versus placebo on CHD, stroke, heart failure and death.

	Studies	Intervention events/participants	Control events/participants	RR (95% CI)
Studies with >6 mm Hg reduction in SBP				
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 mm Hg reduction in SBP				
CHD	2	317/11925	356/11920	0.90 (0.77-1.03)
Stroke	2	290/11925	312/11920	0.93 (0.80-1.10)
Heart failure	1	21/6356	29 / 6349	0.72 (0.41-1.27)
Death	2	750/11925	820/11920	0.91 (0.83-1.00)
All studies				
CHD	13	492/17510	596/17614	0.84 (0.74-0.94)
Stroke	13	600/17594	830/17614	0.73 (0.66-0.80)
Heart failure	9	87/9528	186/10228	0.52 (0.40-0.67)
Death	13	1249/17521	1447/17614	0.87 (0.80-0.93)

RR = risk ratio; CI = confidence interval; SBP = systolic blood pressure.

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 are recommended first-line antihypertensive therapies 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:	Quintiles IMS 2015 and 2016 sales data presented in the application indicates lisinopril+HCTZ (strength unspecified) to be the more commonly prescribed ACE inhibitor + diuretic combination, with the lowest average price per pill (EUR 0.07-0.08 – close to equivalent in US$). According to the MSH International Drug Price Indicator Guide, in 2014, the median buyer prices per tablet for lisinopril 10 mg and HCTZ 25 mg were US$ 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 to non-communicable diseases (NCDs). The Committee also noted that pharmacological management for NCDs is complex and 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 minimize the development of resistance. Combination therapy is often essential in these conditions and components should not be given individually, thus 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 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 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 (28). 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 multi-drug therapy of cardiovascular disease. However, the Committee also recognised that particularly for patients on established multi–medicine regimens, moving to a FDC containing these products would likely improve adherence and that therefore there should be discretion at national level to make this choice.
Committee Recommendations: **(draft for EC consideration)**	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. The Committee 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 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 non-communicable 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 (ARBs), 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 (ACE-I).
Applicant:	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 (McMaster University Faculty of Health Sciences, Hamilton, Canada).
WHO Technical Department:	Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention
EML / EMLc	EML
Section:	12.3 Antihypertensive medicines, 12.4 Medicines used in heart failure
Dose form(s) & strengths(s):	Tablet: 25 mg; 50 mg; 100 mg
Core / Complementary:	Core
Individual / Square box listing:	Square box
Background: (if relevant, eg. resubmission, previous EC consideration)	ARBs had not previously been considered for inclusion on the EML. Angiotensin-converting-enzyme inhibitors (ACE-I) 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-I. 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-I and ARBs are widely recommended in international evidence-based guidelines for the treatment of hypertension, treatment of 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 (JNC-8) recommend the use of ARBs or ACE-I 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-I or ARBs for persons with diabetes and hypertension, especially with concomitant coronary artery disease to reduce morbidity and

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	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-I intolerant (7, 8). The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines for evaluation and management of CKD recommends either an ARB or ACE-I for all persons with CKD with urine albumin excretion of more than 300 mg per day, to prevent and control proteinuria and consequent nephropathy (9).
Summary of evidence: benefits **(from the application)**	The application stated that considerable high-quality data have demonstrated the efficacy of ACE-I for the treatment of hypertension as well as primary and secondary prevention of 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 as ACE-I, inhibiting the renin-angiotensin system by blocking renal receptors for angiotensin instead of preventing its generation in the lung. <u>Hypertension</u> Matchar et al found no significant difference in blood pressure lowering between ACE-I and ARBs in a systematic review of 61 studies involving more than 15,000 patients (13). A 2014 Cochrane systematic review examined nine studies with 11,007 participants and found no significant difference between ACE-I 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). <u>Heart failure</u> ACE-I and ARBs are efficacious in secondary prevention of morbidity and mortality in patients with existing heart failure with reduced ejection fraction. A meta-analysis by Flather et al. (16) of five trials, involving 12,763 patients with heart failure with reduced ejection fraction found that use of an ACE-I substantially decreased risk of all-cause death, readmission for heart failure, and myocardial infarction. A randomized trial of the ARB valsartan in chronic heart failure found, similarly, a significant decrease in mortality and morbidity; signs and symptoms of heart failure; and hospitalizations for treatment relative to placebo (17). Another trial by the VALIANT investigators showed non-inferiority of valsartan compared to captopril among patients with post-myocardial infarction with reduced ejection fraction (18). The application stated that based on these data and others, the 2013 American College of Cardiology/American Heart Association Guideline for the Management of Heart Failure and the 2016 European Society of Cardiology 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-I intolerant (7, 8). <u>Chronic kidney disease (CKD)</u> ACE-I and ARBs may be superior to other anti-hypertensives in the secondary prevention of cardiovascular events in persons with CKD because, in addition to their impact on blood pressure control, these medications influence other renal sequelae, such as proteinuria. A meta-analysis of the effect of monotherapy and combination therapy with ACE-I and ARBs for CKD in 6,181 participants (18) found that both significantly reduced proteinuria relative to both placebo and calcium channel blockers (RR 0.66, 95% CI 0.63-0.69 and 0.62, 95% CI 0.55-0.7, respectively) over 5 to 12 months and that both were equally effective.

	The European Society of Cardiology and European Association for the Study of Diabetes guidelines on diabetes, pre-diabetes, and cardiovascular disease therefore recommend ACE-I and ARB for secondary prevention of CVD in persons with these conditions (6).
Summary of evidence: harms (from the application)	ACE-I frequently cause cough secondary to increased bradykinin because of ACE-I-mediated inhibition of pulmonary kininase activity (19-21). In addition, ACE-I can cause angioedema in 0.1% to 0.8% of individuals, with an increased rate of up to fivefold in people of African descent (10, 11, 22, 23). Rates of adverse events with ARBs have been assessed relative to placebo and to ACE-I. 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% versus 4.2%) and angioedema (0.1% versus 0.3%) with telmisartan compared to ramipril (10). The rate of hyperkalemia was comparable in both groups (3% and 3% for ramipril and telmisartan, respectively). The TRANSCEND investigators examined 5,926 patients deemed intolerant to ACE-I 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 in these side effects when compared to the placebo group (12). Both ACE-I and ARBs are contraindicated in pregnancy – ARBs due in part to feedback disinhibition of renin release that 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), and 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-I (Relative Risk 0.83, 95% CI 0.74-0.93), mostly due to 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-I was 0.72 (95% CI 0.85-0.81), suggesting that ARBs are better tolerated than ACE-I (15).
Additional evidence: (not in the application)	N/A
WHO Guidelines:	N/A
Costs / cost-effectiveness:	Generic formulations of ARBs are now available, making the differences in costs between ARBs and ACE-I smaller over time. 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 with gradual decreases in prices thereafter. By way of comparison, the median buyer price for losartan 50 mg according to the MSH Drug Price Indicator Guide (2015) was US$ 0.0181 per tablet/capsule, while the median buyer price for enalapril 20 mg was US$ 0.0114 per tablet/capsule.
Availability:	ARBs have been approved by stringent regulatory authorities including the FDA (USA), European Medicines Agency, Australian Therapeutic Goods Administration, Japan Pharmaceuticals and Medical Devices Agency, and the Canadian regulatory agency.
Other considerations:	N/A
Committee Recommendations:	The Expert Committee noted that there is evidence of a favourable benefit to risk profile with the use of losartan for treatment of hypertension. The Expert 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 sub-section)

Aspirin + atorvastatin + ramipril – addition – EML

Aspirin + atorvastatin + ramipril	**ATC Code: C10BX06**
Proposal:	The application proposed the addition of a fixed-dose combination (FDC) formulation of aspirin, atorvastatin and ramipril to the core list of the EML for the secondary prevention of cardiovascular disease (CVD).
Applicant:	Dr Oyere Onuma, WHO, Management of Noncommunicable Diseases Unit
WHO Technical Department:	Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention
EML / EMLc	EML
Section:	12.7 Fixed-dose combinations of cardiovascular medicines (NEW)
Dose form(s) & strengths(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
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 ACE inhibitor The intention of square box listings is to limit options to alternatives within the same pharmacological class. A similar 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. Therefore, it may not be appropriate include a square box against the ACEI 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 ACEI component.
Background: (if relevant, eg. resubmission, previous EC consideration)	This was the third time an application had been made for inclusion on the EML of a FDC formulation for secondary prevention of CVD. Previous applications were considered by the Expert Committee in 2013 and 2015. From the report of the2013 Expert Committee (1): The 2013 application made reference to three FDC formulations of varying combinations and strengths. It was unclear to the Expert Committee which of the combinations/strengths was being proposed for inclusion in the EML. The Expert Committee noted that there was a need for access to effective and appropriate secondary prophylaxis for cardiovascular diseases. Although there is wide acceptance of the concept of using a fixed-dose combination for the prevention of cardiovascular disease, the proposal did not present a comprehensive review of the projected health gains from use of any of the fixed dose combinations 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

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	the fixed-dose combinations that was powered to show a difference in morbidity and mortality. While the medicines in the proposed fixed dose combinations 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 a fixed-dose combination as opposed to multiple separate agents. However, the Committee also noted that previous reviews of the effect of fixed-dose combinations on adherence in other therapeutic areas such as HIV and malaria may not be directly relevant to the potential adherence outcomes in patients with cardiovascular disease. In addition, there was no evidence to substantiate the claim that widespread use of the proposed fixed-dose combinations 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 fixed-dose combination formulations. Only one of the three dosage forms listed had undergone a bioavailability study comparing the individual components with the fixed-dose combination (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 fixed-dose combinations for the prevention of cardiovascular disease is a promising concept and that a further submission should be made once adequate clinical trials are available and the choice of formulation is clear. The 2013 application, expert reviews and supporting documents are available at http://www.who.int/selection_medicines/committees/expert/19/applications/polypill/en/ From the report of the 2015 Expert Committee (5): The 2015 application requested inclusion of one or more of combination products and proposed listing as a therapeutic group with a square box symbol, allowing use of different combinations and formulations. 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 cardiovascular disease (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% 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 nine 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 (75 mg aspirin, 20 mg simvastatin, 10 mg lisinopril and 12.5 mg hydrochlorothiazide) and standard care (not defined) in terms of reductions in systolic blood pressure, total cholesterol or 10-year risk of cardiovascular disease: 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 ≥ 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% versus 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% versus 11.5%; RR 1.26; 95% CI 1.02–1.55) (968). These results were consistent with the meta-analysis by Elley et al. (10) and present 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) versus 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 cardiovascular

	disease. The Expert Committee acknowledged the potential advantages of FDCs for improving adherence and for providing an affordable product for secondary prevention of cardiovascular diseases. 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 cardiovascular disease 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 over 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 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 3,140 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 to the usual care arm for the primary study end points, patients in the polypill arm had higher self-reported adherence to combination therapy (80% versus 50%, relative risk (RR) 1.58; 95% CI, 1.32 to 1.90), lower systolic blood pressure (-2.5 mmHg; 95% CI: −4.5 to −0.4) and lower LDL-cholesterol e (−0.09 mmol/L; 95% CI: −0.18 to 0.00). The greatest effects were observed in those patients who were under-treated at baseline. The primary endpoint 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 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% versus 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 3,080 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 submission summarised 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. Adherence (measured by different methods between the studies), when reported, 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 summarised 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 of the meta-analyses by de Cates and Elley (6, 10).

Additionally, the current application described safety findings from the same five trials noted above. No statistically significant differences were observed (or were not reported) between FDC and control arms in the proportion of patients experiencing at least one serious adverse event. Treatment discontinuations due to adverse events reported in the FOCUS trial were 4% in both FDC and components administered separately treatment arms (8).

Additional evidence: (not in the application)

A Public Assessment Report of the application made by Ferrer International (manufacturer of Trinomia) for marketing authorisation 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 coadministered component monotherapy in healthy adults. The test product (FDC) was found to be equivalent to the reference (components) with respect to the extent and rate of absorption based on statistical analysis.

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 ramipril) has been evaluated for reimbursement in Europe through National Health Services in Belgium (*Commission de remboursement des médicaments*), Greece (*Social Security Institute*), Ireland (*Primary Care Reimbursement Service*), Portugal (*Autoridade Nacional do Medicamento e Produtos de Saúde*) and Spain (*Inter-Ministerial Pricing Commission*).

The ex-factory prices for 1-month treatment of the FDC, and the sum of its components in each country are shown in the table below.

Country	Trinomia AAR 100/20/2.5 28 capsules		Trinomia AAR 100/20/5 28 capsules		Trinomia AAR 100/20/10 28 capsules	
	Sum mono-components	Approved	Sum mono-components	Approved	Sum mono-components	Approved
Belgium	7,14 €	8,37 €	8,60 €	9,87 €	11,84 €	12,97 €
Greece	16,88 €	8,21 €	18,12 €	9,68 €	19,21 €	12,72 €
Ireland	9,07 €	8,37 €	9,83 €	9,87 €	11,0 €	12,97 €
Portugal	8,88 €	8,37 €	9,49 €	9,87 €	12,71 €	12,97 €
Spain	8,37 €	8,37 €	9,87 €	9,87 €	12,97 €	12,97 €

WHO Guidelines:

The 2007 WHO *Pocket Guidelines for Assessment and Management of Cardiovascular Risk* (19) recommendations 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 United States 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 FDC therapy was a cost-effective strategy for preventing fatal and non-fatal cardiovascular events (23). The model's base case 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 by Becerra et al. compared the cost-effectiveness of FDC treatment with multiple component monotherapy

	over 10 years (24). The analysis 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 (NNT) with FDC therapy was 22.2 and 45.4 to avoid a nonfatal and fatal cardiovascular event, respectively. The analysis concluded FDC therapy to be a cost-effective treatment strategy. Comparative information regarding the cost of the FDC and the sum of its components was requested from the applicant by the Secretariat (see above).
Availability:	Ferrer Interncional, S.A., Spain
Other considerations:	The Expert Committee noted differences between the use of FDC therapies for treatment of communicable diseases compared to non-communicable diseases (NCDs). The Committee also noted that pharmacological management for NCDs is complex and 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 minimize the development of resistance. Combination therapy is often essential in these conditions and components should not be given individually, thus 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 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 currently at least 14 different combination products are 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 multi-drug therapy of cardiovascular disease. However, the Committee also recognised that particularly for patients on established multi–medicine regimens, moving to a FDC containing these products would likely improve adherence and that therefore there should 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 (FDC) formulation of aspirin, atorvastatin and 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 non-communicable 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 – addition – EML and EMLc

Hypochlorous acid	**ATC Code: DO8AX07** (sodium hypochlorite)
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:	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) & strengths(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.
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 specialised wound dressings, nor 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 associated with considerable morbidity and healthcare 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. Systemic antibiotics are indicated only in particular circumstances (e.g., systemic sepsis, cellulitis) (1). The use of topical biocides is a preventative control measure against the spread of nosocomial infections and multi-drug resistant bacteria within hospital and other healthcare 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 compared with various comparators in the management different infectious wound types including diabetic foot ulcers, chronic wounds, post-operative wounds, and peritonitis (2-18). No assessment was undertaken of the quality of the studies and there appeared to be considerable heterogeneity in terms of interventions, comparators and outcomes measured. No systematic-reviews were identified nor conducted. As general overview, the studies appeared to show improved efficacy for patients treated with hydrochlorous acid solution compared to the comparator group for outcomes including wound size, purulent discharge, appearance of granulation and epithelisation, length of hospital stay, signs of infection etc. The majority of the studies involved hypochlorous acid solution and did not provide information about the hydrogel formulation. The 2016 International Wound Infection Institute (IWII) Consensus Guidelines 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)	Limited information regarding the safety of hypochlorous acid solution in clinical use is provided in the application. The application 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. An RCT of 45 patients with infected diabetic foot ulcers treated with 'neutral pH super oxidised aqueous solution' (NpHSS) or standard care found NpHSS to be associated with less cytotoxicity and tissue 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, but a higher frequency of reinfection 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. The preparation of these guidelines is acknowledged as supported by the World Health Organisation (WHO). The Guidelines were not referenced in the application, nor were copies available for review.
Costs / cost-effectiveness:	The proposed pricing by the applicant of hypochlorous acid solution is US$ 5.52 per 500 mL (equivalent to US$ 0.011 per mL). In comparison, the median price for povidone iodine 10% solution according to the MSH International Drug Price Indicator Guide is US$ 0.0087 per mL. Prices of povidone iodine 10% quoted in the application range from US$ 0.0134 per mL (Fiji) to US$0.0946 per mL (Australia). The proposed pricing by the applicant of hypochlorous acid hydrogel is US$ 6.00 per 250 g (equivalent to US$ 0.024 per g). Comparator prices for alternative hydrogels are quoted as ranging from US$ 0.1927 to 0.452 per mL (New Zealand).
Availability:	The application stated that hypochlorous acid solution is available under the trade names Electromicyn, Microcyn, Dermacyn, MicroSafe, Microdacyn and Oxum in North America, Central America, South America, Middle East, India, Europe, Pacific Islands, and Asia.
Other considerations:	The Committee noted that the product was classified by regulatory agencies in some countries (e.g., US Food and Drug Administration, European Medicines Agency, Australian Therapeutic Goods 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: (draft for EC consideration)	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 the uncertain quality of evidence presented in the application for the solution and that no evidence was presented in the application 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 (UPA) to the core list of EML for emergency contraception (EC) within 5 days of unprotected sexual intercourse or contraceptive failure in women of reproductive age.
Applicant:	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) & strengths(s):	Tablet: 30mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 healthcare services, including for 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% ended in miscarriage, and 38% resulted in an unplanned birth (2). In developing countries, it corresponds to 74 million unintended pregnancies due to the lack of use of effective method of regular contraception (70%) and due to contraceptive failure (30%), such as missed pills, broken or slipped condoms (3, 4). In 2016, of the 20 million pregnancies occurring in adolescents aged 15 to 19 years living in developing countries, approximately 50% were unintended (5). Maternal causes are the second highest ranked cause of mortality at this age group globally (6). In developing countries, the current use of EC is relatively low. Of the women who are sexually active, 3% reported having ever used an EC (7). Unintended pregnancies are usually associated with negative health, financial, social and emotional consequences. In 2012, about 50% of the unintended pregnancies ended in induced abortion (2). In 2003, an estimated 42 million pregnancies were voluntarily terminated, 20 million unsafely, with risks to health and endangering 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 (9, 10) that compared UPA-EC and LNG-EC in 1,716 women with regular menses requesting EC following unprotected intercourse. 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%CI 0.35 to 0.99; p=0.04). When comparing UPA-EC and LNG-EC used within 72 hours of unprotected sexual intercourse (UPSI), UPA-EC was

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	shown to be more effective, although the difference was considered marginally significant (RR=0.63; 95%CI 0.37 to 1.07; p=0.089) (8). When using a logistic-regression model taking into account known confounding factors that may alter the treatment effect, the meta-analysis by Glasier et al showed the odds of pregnancy were significantly lower (p<0.05) among women who used UPA-EC than LNG-EC, taken within 24, 72 and 120 hours of UPSI (9). Results from a pooled analysis of three pharmacodynamic studies where EC treatment was given at a late follicular stage (follicle ≥ 18 mm diameter) showed that when EC is administered before the LH peak, UPA-EC was significantly better than LNG-EC (1.5 mg) at delaying follicular rupture by 5 days, whether treatment was administered before the LH surge (RR=4; 95%CI 1.5 to 10.7; p=0.0026) or after the LH surge but before the LH peak (RR=55.5; 95%CI 1.5 to 20.4; p=0.0018). No treatment was effective at postponing follicular rupture when given at the time of the LH peak (11). <u>Efficacy in obese patients</u> Pooled data from two RCTs comparing UPA-EC and LNG-EC assessed risk of pregnancy in women categorised by body mass index (BMI) (12). Results showed that pregnancy risk was doubled in overweight women who took LNG-EC in comparison to normal or underweight women (odds ratio (OR)=2.09; 95%CI 0.86 to 4.87; ns), and more than 4 times greater in obese women (OR=4.41; 95%CI 2.05 to 9.44; p=0.0002). Among the women who took UPA-EC, the risk of pregnancy in overweight women did not differ from the risk for women with BMI<25 kg/m² (OR=0.97; 95%CI 0.27 to 2.83; ns) and the risk of pregnancy in obese women who took UPA-EC was higher but not statistically significant (OR=2.62; 95%CI 0.89 to 7.00; ns). <u>Efficacy in adolescent patients</u> As part of the Paediatric Investigation Plan agreed with the 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 which 76 were under 16 years). In the efficacy-analysis population, pregnancy occurred in 7 women (of which 2 were under 16 years), yielding a pregnancy of 1.5%, a rate similar to that observed in adult women (13).
Summary of evidence: harms **(from the application)**	Cheng et al. provided safety data by comparing adverse events (AEs) following the intake of UPA-EC (n=1,879) and LNG-EC (n=1,891): no differences between the two treatments were found. The most frequent AEs were nausea, vomiting, breast tenderness, headache, dizziness, fatigue, abdominal pain, diarrhoea, spotting /bleeding after treatment, dysmenorrhea and back pain (8). A meta-analysis of phase III RCTs (2,221 women) and post-marketing experience (1.4 million women) reported only 2 serious adverse drug reactions 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 less than 18 years old (13). The most frequent AEs were headache, nausea and abdominal pain, changes in cycle duration and menorrhagia.. These data indicate that safety profile observed in adolescents is similar to that observed in adults. Jesam et al. assessed safety and tolerability of repeated use of UPA-EC within the same menstrual cycle. Most frequent AEs were headache, nasopharyngitis, influenza and mild anaemia. All AEs 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 (MEC) for Contraceptive Use (17), the Selected practice recommendations (SPR) for contraceptive use, and will be included in

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	the Family Planning Global Handbook for Providers.
Costs / cost-effectiveness:	UPA-EC costs approximately €15 to 57 in Europe and $40 to 70 in the US. The manufacturer, HRA Pharma has proposed tiered-pricing strategies to provide sustainable and affordable access. The cost-effectiveness of UPA-EC versus 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, for example in the UK, 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 in the UK (£948), regardless of the outcome (19).
Availability:	HRA Pharma. 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 EU where was approved by EMA since 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 based on 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 – 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 (DPMA-SC) 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 differentiate its route of administration as intramuscular.
Applicant:	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 administered in alignment with current WHO guidelines.
EML / EMLc	EML
Section:	18.3.2 Injectable hormonal contraceptives
Dose form(s) & strengths(s):	Injection (subcutaneous): 104 mg/0.65 mL in pre-filled syringe or injection delivery system
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Depot medroxyprogesterone acetate for intramuscular 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 the 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 DMPA-SC as reported by Jain et al. (4). In each study, participants received contraceptive injection every 3 months for up to 1 year. There were a combined total of 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 endpoint) 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. The 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 listing. The overall safety profile of DMPD-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 of DMPA-IM and include bleeding irregularities, amenorrhea, weight gain, headache, and mild, reversible loss of bone mineral density with. 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 including 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's *Medical eligibility criteria for contraceptive use* (7) state that DPMA-IM and DMPA-SC appear therapeutically equivalent, demonstrating similar pharmacokinetics, effects on serum estradiol levels and high contraceptive efficacy. It recommends all recommendations for DMPA-SC should follow the current recommendations for DMPA-IM (very low quality evidence).
Costs / cost-effectiveness:	The unit price for subcutaneously administered depot medroxyprogesterone acetate 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. DMPA-IM, in comparison, has a reported median supplier price of US$ 0.75 per unit according to the International Drug Price Indicator Guide.
Availability:	Pfizer Ltd.
Other considerations:	Comments on the application received from Médecins Sans Frontières (MSF) indicated that MSF did not support addition of this SC formulation to the EML based on an anticipated low probability of programs involving self-administration and the additional cost in resource-limited settings compared to the IM formulation.
Committee Recommendations:	The Expert Committee recommended the addition of the subcutaneous injection formulation of medroxyprogesterone acetate to the core list of the EML. The Committee considered that the SC formulation, with appropriate training for administration, would provide an effective, safe and convenient contraceptive treatment choice. The ability to self-administer may be an advantage in settings where there is limited availability of health care providers. The Committee also recommended the current listing of the IM formulation be amended as proposed in the application, to clarify its route of administration as intramuscular.

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18.5 Insulins and other medicines used for diabetes

Long-acting insulin analogues (addition) – EML and EMLc

Insulin glargine **Insulin detemir**	**ATC Code: A10AE04** **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, insulin glargine was proposed to be listed with a square box as representative of the class, with alternatives limited to insulin detemir and biosimilar insulin glargine (Basaglar).
Applicant:	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
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) & strengths(s):	All insulins come dissolved or suspended in liquids. The standard and most commonly used strength in most countries is U-100, which means it has 100 units of insulin per milliliter of fluid.
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, eg. resubmission, previous EC consideration)	In 1982 the FDA approved human insulin produced using gene technology, as substitute for chromatographic purification techniques of highly purified animal insulin. In 1985 the WHO Expert Committee on the Selection and Use of Essential Medicines approved the inclusion of isophane NPH (neutral protamine Hagedorn) insulin. Since 1996, different insulin analogues, altered form of human insulins, have been introduced worldwide and they are characterized by various pharmacokinetics (absorption, distribution, metabolism, and excretion characteristics). 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, with an uncertain cost-effective profile. Since 2011 additional evidence became available.
Public health relevance: (burden of disease)	Diabetes and its complications are some of the leading causes for premature mortality with 3.7 million deaths reported in 2012 (1). The prevalence of diabetes has nearly doubled worldwide since 1980 (1) and accounts for 14.5% all-cause mortality in people aged 20 to 79 years, with the number of cases of type 1 diabetes on the rise 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 the use of medications to help control blood glucose levels. All people living with type 1 diabetes need insulin as well as more than 10% of people with

	type 2 diabetes (3).
Summary of evidence: benefits (from the application)	Evidence presented was based on a systematic review and network meta-analysis that examined the comparative safety, effectiveness, and cost-effectiveness of long-acting insulin - branded medicinal products glargine and detemir - compared to intermediate-acting insulin in patients with type 1 diabetes. The review and its protocol were funded by the British Columbia Ministry of Health and published in medical journals (4, 5). A total of 38 relevant studies and one companion report were included in the review, including 27 RCTs representing 7,496 patients. Glycosylated hemoglobin (A1c) was the primary outcome. Glargine once daily, and detemir once daily statistically significantly reduced A1c compared to NPH once daily (low quality of evidence) (mean difference (MD) glargine: -0.5, 95% CI -0.87, -0.13; MD detemir: -0.16, 95% CI -0.3, -0.03). When compared to NPH twice or more daily, insulin analogues were not associated with a decrease in A1c. In a subgroup analysis by baseline A1c, glargine and detemir once daily were found to be statistically significantly more effective compared to NPH once daily for patients with poorly controlled diabetes (A1c>8%). The decrease in A1c was not different between glargine and detemir (low to moderate quality of evidence). For weight gain, patients receiving detemir once or twice daily, detemir once daily, and glargine once daily, had significantly less weight gain than those receiving NPH once daily. Patients experienced statistically significantly more weight gain with NPH once daily and detemir once daily when compared with NPH once or twice daily; however, detemir once or twice daily resulted in statistically significantly less weight gain than NPH once or twice daily. Differences were often in the order of 5 kilos. For serious hyperglycemia, retinopathy, transient ischemic attack, death due to myocardial infarction, death due to cardiopulmonary arrest, all-cause mortality, pancreatic cancer, uterine cancer and quality-of-life, direct comparisons meta-analyses comparing glargine and detemir to NPH did not reached statistical significance.
Summary of evidence: harms (from the application)	Insulins are hypoglycemia-inducing agents. There is evidence that hypoglycemia may adversely affect the cardiovascular risk profile, in particular in older people and subjects affected by a longer duration of diabetes (6). Overall, published trials show severe hypoglycemia may increase cardiovascular mortality (7, 8). Preventing hypoglycemia is as important, or more important for disease management and long-term prognosis, than tight glycemic control. Evidence for safety was based on the previously mentioned systematic review and network meta-analysis (5). Statistically significantly fewer episodes of severe hypoglycemia were experienced by patients receiving detemir once or twice daily compared to NPH once or twice daily (odds ratio (OR) 0.62, 95% confidence interval 0.42 to 0.91). In one RCT, glargine once daily was associated with a statistically significant increase in episodes of severe hypogycemia compared to detemir once or twice daily (OR 4.30, 95% CI 1.19 to 15.53). However, these findings were no longer statistically significant in the network meta-analysis.
Additional evidence: (not in the application)	N/A
WHO Guidelines:	WHO guidelines on hypoglycaemic agents, including insulin analogues, are currently in development. The application refers to other systematic reviews and guidelines on top of the network meta-analysis. Four previous systematic reviews, published between 2007 and 2011, compared the safety and effectiveness of long acting insulin analogs to intermediate acting insulin in patients with type 1 diabetes (9-12). For the outcome of A1c, Vardi (2008) and Monami (2009) concluded that long acting insulins are probably slightly superior to intermediate acting insulin. However, the network meta-analysis conducted by Sanches (2011) found no statistically significant difference between the insulin groups. Heterogeneity prevented the pooling of studies in the Tran (2007) systematic review for this outcome.

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	Similar to this application results, one review (12) found that long acting insulin was associated with a statistically significant reduction in the risk of severe hypoglycemia when compared to NPH. The other three reviews (9-11) found no statistically significant differences between the groups for this outcome. In addition to these systematic reviews, a recent clinical guideline commissioned by the National Institute for Health and Care Excellence 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 hypoglycemia and body weight reduction.
Costs / cost-effectiveness:	In total, 10 studies were included focussing on 3 comparisons: glargine versus NPH, detemir versus NPH, and glargine versus 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 QALYs. Both of these were from one study that reported receiving financial contributions from Sanofi-Aventis. Of the six analyses (14, 15, 17, 18) that found glargine to be more costly and more effective than NPH, one of these studies received funding from Health Canada, and two studies received funding 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. Fourteen cost-effectiveness analyses in five studies (14, 19-22) reported a comparison between detemir and NPH. Three of these analyses found that detemir was less costly and more effective in one study that received funding from Novo Nordisk. The rest of the analyses found that detemir was more costly but also more effective than NPH. One of these studies was funded by Health Canada and the other four were funded by Novo Nordisk. 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. Compared to detemir, glargine was less costly and less effective (in term of both life years and quality-adjusted life years [QALY]) from the societal perspective in one study that received an unrestricted grant from Novo Nordisk Inc. (23).
Availability:	Lack of access to affordable insulin is a problem globally with over half of the people who need insulin not able to afford or access it leading to health complications and early death (1, 3). Access to Insulin compared to other non-communicable disease medications was found to be 2.5 to 45 times higher priced (3). The annual cost of insulin was $736 for each patient in the US in 2013 which was a threefold increase from 2002. Medications for diabetes are the second most expensive category of prescription drugs in the US and huge burden to health budgets (24). 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 with the indication of treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. Patent protection of long acting insulin analogues is expiring or will soon expiring in US, Europe and other countries. As the patent expiry dates of the long-acting insulin analogs are approaching in some countries, there is increasing interest in the potential of basal or long-acting biosimilar insulins. In 2014 EMA approved Abasaglar as a biosmilar of the biological reference medicine Lantus 2007. In 2015 Basaglar was approved by the FDA as a follow-on biologic of insulin glargine treatment. Copies of the long-acting insulin glargine have been approved and brought onto the market in several countries, such as India, the People's Republic of China, Pakistan, Mexico, and Kenya.
Other considerations:	The costs of long acting insulin appeared to be greater than those of intermediate acting

	insulin; however, the application reported instances where the long acting insulin was actually less costly than the intermediate acting insulin. Most importantly, if the price of long acting insulin were to reduce, the probability that they will be cost-effective compared to NPH may increase (25). When biosimilar erythropoietins were approved, the price declined by 20% in a relatively short period of time (i.e. 3 years) (26). Others studies report a total decline of 30-40% since the market introduction of biosimilar epos (27). Biosimilar insulins have the potential to reduce treatment costs, and therefore improve access for patients, physicians, and health care systems.
Committee Recommendations:	The Expert Committee noted that long acting insulin analogues have been demonstrated to be an effective medication for treating children, young people and adult patients with type 1 diabetes. However, the Committee noted that the magnitude of the benefit provided, compared to human insulin, was not large. The Committee considered that the benefits in terms of reduced A1c and advantages of reduced hypoglycaemia of insulin analogues over human insulin were modest and do not justify the current large difference in price between analogues and human insulin. Based on this evaluation, the Expert Committee therefore 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 (addition) – EML and EMLc

Second-line treatments for type 2 diabetes: **Sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (Table 1)** **Glucagon-like peptide-1 (GLP-1) agonists, basal insulins, bolus insulins and biphasic insulins (Table 2)**	**ATC Code: See 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 (T2D) in adults, adolescents and children: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors (Table 1), GLP-1 agonists, basal insulins, bolus insulins, and biphasic insulins, including analogues (Table 2).
Applicant:	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) & strengths(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, eg. resubmission, previous EC consideration)	In 2013, the Expert Committee on Selection and Use of Essential Medicines evaluated evidence comparing four groups of oral hypoglycaemics: 1. dipeptidyl peptidase-4 (DPP-4) inhibitors, 2. thiazolidinediones, 3. alpha-glucosidase inhibitors, such as acarbose, and 4. meglitinides, against metformin (biguanide) and sulfonylureas (1). 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, alphaglucosidase inhibitors, meglitinides, or thiazolidinediones) offered any efficacy or safety advantages over the existing medicines included in the EML", (i.e. metformin first line and sulfonylurea second line). Since then, a new drug class has entered the market in several countries for the treatment of patients with T2D — sodium-glucose cotransporter-2 (SGLT-2) inhibitors. In addition, a fourth DPP-4 inhibitor (alogliptin) as well as a third GLP-1 analogue (dulaglutide) have appeared and new data on the impact on cardiovascular outcomes of some of the new drugs (e.g., GLP-1 agonists, DDP-4 inhibitors and SGLT-2 inhibitors) have been published. Given the newer agents recently approved in most countries and additional randomized controlled trial (RCT) evidence published over the last 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 systematic review and network meta-analyses of second-line therapies for type 2 diabetes (2).

	In addition, the application reviewed pharmacologic treatments for patients with type 2 diabetes who are at high risk for cardiovascular events. Third-line therapies were not assessed.
Public health relevance: (burden of disease)	Globally, the prevalence of diabetes has nearly quadrupled worldwide since 1980, rising from 108 million to 422 million in the adult population. This trend is associated with an increase in associated risk factors such as overweight and obesity. In 2012, diabetes caused 1.5 million deaths. Additionally, higher than optimal blood glucose caused another 2.2 million deaths, by increasing the risks of cardiovascular and other diseases. Over the past decades, the prevalence of diabetes has risen faster in low- and middle-income countries than in high-income countries (3). Since it is very difficult to distinguish between type 1 diabetes (which requires insulin injections for survival) and type 2 diabetes (where the body cannot properly use the insulin it produces), morbidity data grouped for type 1 and 2 are not available at global or country level. However, the majority of people with diabetes are affected by type 2 diabetes. The WHO Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Setting, including diabetes, provides advice on recommended treatments for diabetes (4). The guidance document is out of date and is scheduled for updating in 2017. Current WHO guidelines recommend initiation of pharmacologic treatment with metformin monotherapy if a target glycated hemoglobin (HbA1c) level is not reached. Most people with T2D will require continuous pharmacologic treatment in order to maintain normal or near-normal glycemic targets, and blood glucose levels may continue to rise gradually over an individuals' life-course. When initial therapy with lifestyle interventions and metformin monotherapy are unsuccessful, a second oral agent (i.e. sulfonylurea) is recommended. This is referred to as second-line therapy or 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 second-line agents because of efficacy, side-effect profiles, long-term safety, and relative cost. However, there are a number of available agents that can be used in combination with metformin: sulfonylureas, 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 been recently 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: Question 1. For adults with type 2 diabetes on metformin monotherapy with inadequate glycemic control, what is the comparative efficacy and safety of using a drug from one of the following classes as second-line agent? a. Sulfonylurea b. Insulin c. DPP-4 inhibitor d. GLP-1 analogue e. SGLT-2 inhibitor Question 2. For adults with type 2 diabetes, what are the comparative cardiovascular effects of drugs belonging to one of the following classes? a. Insulin b. DPP-4 inhibitor c. GLP-1 analogue d. 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 prior to randomization was poorly reported and often unspecified. Patients

using a variety of oral antidiabetes drugs often underwent a run-in period with metformin monotherapy upon trial entry, and were randomized to add-on therapy if glycemic control was inadequate at the end of the run-in period. No studies assessed the effects of switching from metformin to another antidiabetes drug due to intolerable adverse effects, development of contraindications, or inadequate glycemic control. Patients with T2D had a variety of co-morbid conditions. There were some RCTs targeting subgroups of patients with T2D (e.g., microalbuminia, metabolic disorder, dislipidemia) or populations (e.g., restricted to women, caucasian, or patients in a specific geographic 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 endpoints (e.g., HbA1c) versus more clinically meaningful end-points, limited sample sizes, and duration of follow-up. Many RCTs failed to register in a trial registry (e.g., 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., hypoglycemia), true intention-to-treat analyses (i.e., an analysis including all randomized patients), and dose and/or duration of stable metformin therapy prior to randomization. Many studies failed to adequately report details about the dosage of metformin background therapy while on 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 Appendixes of 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 Hemoglobin (HbA1c)
There were 84 RCTs that reported mean change from baseline in HbA1c that 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 for HbA1c. When the classes were compared with each other, DPP-4 inhibitors did not decrease HbA1c as much as sulfonylureas, TZD or GLP-1 agonists (Random effects model, Table A).

Table A: Glycated Hemoglobin (%) - Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI) Ref 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, GLP-1= glucagon-like peptide-1 receptor agonist, INS-BA=basal insulin, INS-BI=biphasic insulin.

Body Weight

There were 70 RCTs that reported changes from baseline in body weight (in kilograms) 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 kg to 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 resulted in significant reductions in mean body weight relative to sulfonylurea (range -1. 9 kg to -4.3 kg) except for TZD. 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 change from baseline. TZD, basal and biphasic insulin added to metformin significantly increased mean body weight change from baseline relative to SGLT-2 inhibitors and GLP-1 agonists (Table B).

Table B: Body Weight in kg - Mean Differences in Change from Baseline for Selected Class Comparisons

Treatment	Reference	MD (95% CrI)
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, GLP-1= glucagon-like peptide-1 receptor agonist, INS-BA=basal insulin, INS-BI=biphasic insulin.

All-cause mortality, cardiovascular mortality and heart failure

The NMA models for all-cause and cardiovascular mortality, and heart failure, were not robust due to the low event rate and the large number of zero events in the data set. Pairwise meta-analyses could not be estimated or found no difference in the relative risks. The estimated confidence intervals were wide, due to the paucity of events. No other direct estimates could be estimated.

Question 2: Patients at high risk for cardiovascular events

For research question 2, 66 articles 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 participants 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 varying background therapies, and pragmatically allowed for continuation of whatever the existing background therapy was at baseline. In general, participants added the study intervention to their existing therapy. Background therapies were: no treatment (i.e. they were drug-naïve and started the study intervention); monotherapy (they were taking a single antidiabetic medication or insulin and added the study intervention to that therapy); dual therapy; and combinations of more than 2 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 (SD3.0) and 32.5 (SD6.3).

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. As all of 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 include protocol amendments made after an interim analysis (EMPA-REG OUTCOME) and a number of participants early censored in the LEADER study.

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 reduced the risk of all-cause mortality. None of the other treatments reduced the risk of all-cause mortality (Table C).

Table C. All-Cause Mortality - Hazard Ratios 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, GLP-1= glucagon-like peptide-1 receptor agonist, TZD= thiazolidinediones.

Cardiovascular Mortality

A total of 6 RCTs (N = 30,439) reported cardiovascular mortality and were included in the reference case analysis. Compared to placebo and to each other, none of the selected classes significantly lowered the risk of cardiovascular mortality (Table D).

Table D. Cardiovascular Mortality - Hazard Ratios 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, GLP-1= glucagon-like peptide-1 receptor agonist, TZD= thiazolidinediones.

Summary of evidence: harms
(from the application)

Question 1: Patients inadequately controlled on metformin

Severe Hypoglycemia

Severe hypoglycemia was typically defined as an event requiring third-party assistance. There were 48 RCTs that reported severe hypoglycemia and were included in the reference case NMA.

None of the classes significantly increased severe hypoglycemia when compared with metformin monotherapy. When compared to each other, the GLP-1 agonists, SGLT and DPP-4 inhibitors significantly reduced the risk of severe hypoglycemia relative to sulfonylureas (Table E).

Table E: Severe Hypoglycemia - Odds Ratios 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)

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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, GLP-1= glucagon-like peptide-1 receptor agonist, INS-BA=basal insulin, INS-BI=biphasic insulin.

Non-Severe Hypoglycemia

There was variability in the clinical definitions of this outcome across the included RCTs. Similar to previous reviews, the most common differences were the specific blood glucose threshold for hypoglycemia and whether or not patients were required to validate symptoms of hypoglycemia with self-monitoring of blood glucose.

A total of 67 RCTs that reported at least one episode of non-severe hypoglycemia that were included in the reference case NMA.

Compared with metformin monotherapy, the odds of non-severe hypoglycemia were higher with sulfonylurea, basal and biphasic insulin. When the classes were compared, all classes except biphasic insulin significantly reduced odds of non-severe hypoglycemia relative to sulfonylurea (Table F). Relative to DPP-4 and SGLT-2 inhibitors and GLP-1 agonists, basal and biphasic insulin significantly increased odds of non-severe hypoglycemia. Biphasic insulin significantly increased odds of non-severe hypoglycemia relative to basal insulin.

Table F: Non-Severe Hypoglycemia - Odds Ratios for Selected Class Comparisons

Treatment	Reference	OR (95% CrI) Ref Case

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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, GLP-1= glucagon-like peptide-1 receptor agonist, INS-BA=basal insulin, INS-BI=biphasic insulin.

Severe Adverse Events

There were 66 RCTs that 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 odds of serious adverse events (Table G).

Table G: Serious Adverse Events - Odds Ratios 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)

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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, GLP-1= glucagon-like peptide-1 receptor agonist, INS-BA=basal insulin, INS-BI=biphasic insulin.

Question 2: Patients at high risk for cardiovascular events

Severe Hypoglycemia

A total of eight RCTs reported severe hypoglycemia (N =66,133) and were included in the reference case NMA. The percentage of participants with a severe hypoglycemic event ranged from 0.3% to 3.3%. Compared with placebo, GLP-1 agonists there were significantly less risk of severe hypoglycemia but a significantly increased risk with TZD. There was a significantly lower risk of severe hypoglycemia with GLP-1 agonists relative to DPP-4 inhibitors. TZD significantly increased risk of severe hypoglycemic events relative to both DPP-4 inhibitors and GLP-1 agonists, but did not significantly differ in risk from SGLT-2 inhibitors (Table H).

Table H. Severe Hypoglycemia – Odds Ratios for All Class Comparisons

Treatment	Reference	OR (95% CrI)
DPP-4	Placebo	1.18 (0.91,1.54)

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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, GLP-1= glucagon-like peptide-1 receptor agonist, TZD= thiazolidinediones.

Severe Adverse Events

A total of 6 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 to 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	

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	Deviance Information Criteria 117.501

SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD= thiazolidinediones.

In synthesis, based on network meta-analyses, adjunctive second-line therapies were associated with possible reductions in glycemic control when compared to metformin monotherapy, with few differences between any of the active treatments. Sulfonylurea and GLP-1 analogues decreased glycated hemoglobin when compared to DPP-4; GLP-1 analogues and sulfonylurea decreased weight when compared to metformin monotherapy, while insulin and sulfonylurea increased weight when compared with the other classes. GLP-1 analogues and insulins increased the number of adverse events and withdrawals. In high risk patients, SGLT-2 were possibly associated with a reduction in all-cause mortality when compared to placebo and to DPP-4 analogues, and SGLT-2 were not associated with severe hypoglycemia events.

Sulfonylurea and insulins increased non-severe hypoglycemia when compared to metformin monotherapy and other classes. However basal insulin was associated with fewer non-severe hypoglycemia events when compared to sulfonylurea.

Additional evidence: (not in the application)	N/A
WHO Guidelines:	WHO guidelines on type 2 diabetes are in development, but were not finalized at the time of the Expert Committee meeting.
Costs / cost-effectiveness:	The application did not provide information on costs of medicines or 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 and harms for some of the medicines covered in the application will be supplemented in the following years as new trials and longer follow up are completed. The Committee considered the evidence provided was insufficient to propose changes to the Model List, which up to now 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 T2D. 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, prior to selectively supporting this class of medicines in patients with type 2 diabetes. Based on the evaluation, the Expert Committee therefore did not recommend to add any additional medicines for second line therapy of T2D

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Table 1: Oral medicines

Drug Class	INN Drug Name	Anatomical Therapeutic Chemical (ATC) codes	Dose form(s) & strengths(s)	DDD
Single Drug Products				
DPP-4 Inhibitors	Alogliptin	A10BH04	Tab, 6.25 mg, 12.5, 25	25 mg
	Linagliptin	A10BH05	Tab, 5 mg	5 mg
	Saxagliptin	A10BH03	Tab, 2,5 mg, 5	5 mg
	Sitagliptin	A10BH01	Tab, 25 mg, 50, 100	100 mg
SGLT-2 Inhibitors	Canagliflozin	A10BK02	Tab, 100 mg, 300	200 mg
	Dapagliflozin	A10BK01	Tab, 5 mg, 10	10 mg
	Empagliflozin[a]	A10BK03	Tab, 10 mg, 25	17.5 mg
Sulfonylureas	Chlorpropamide	A10BB02	Tab, 100 mg, 250	375 mg
	Gliclazide[b]	A10BB02	Tab, 40 mg, 80	160 mg
				60 mg
	Glimepiride [b]	A10BB12	Tab, 1 mg, 2, 3, 4	2 mg
	Glibenclamide/Glyburide [b]	A10BB04	Tab, 2,5 mg, 5	10 mg
	Tolbutamide	A10BB03	Tab, 500 mg	1,500 mg
TZDs	Pioglitazone	A10BG03	Tab, 15 mg, 30, 45	30 mg
	Rosiglitazone	A10BG02	Tab, 4 mg, 8	6 mg
Meglitinides	Nateglinide	A10BX03	Tab, 60 mg, 120, 180	360 mg
	Repaglinide	A10BX02	Tab, 500 microg, 1 mg, 2 mg	4 mg
AGIs	Acarbose	A10BF01	Tab, 50 mg, 100	300 mg
Fixed-Dose Combination Drug Products				
DPP-4 Inhibitors/Biguanides	Alogliptin/metformin	A10BD13	Tab, alogliptin 12.5, metformin 500 mg, 12.5/850, 12.5/1000	25 mg
	Linagliptin/metformin	A10BD19	Tab, linagliptin 2.5, metformin 500 mg, 2.5/850, 2.5/1000	5 mg
	Saxagliptin/metformin	A10BD21	Tab, saxagliptin 2.5, metformin 1000 mg, 5/500, 5/1000	5 mg

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	Sitagliptin/metformin	A10BD07	Tab, sitagliptin 50, metformin 500 mg, 50/850, 50/1000, 100/1000	100 mg
SGLT-2 Inhibitors/Biguanides	Dapagliflozin/metformin	A10BD15	Tab, dapagliflozin 5, metformin 850 mg, 5/1000	10 mg
	Empagliflozin/metformin	A10BD20	Tab, empagliflozin 12.5, metformin 850 mg, 5/850, 12.5/1000, 5/1000	17.5 mg
	Canagliflozin/metformin[c]	A10BD16	Tab, canagliflozin 50, metformin 850 mg, 50/1000	200 mg

a Not included in Therapeutic Choices.

b Generic products also available.

c Pre-Notice of Compliance CADTH Common Drug Review submission received on February 3, 2016 (https://www.cadth.ca/canagliflozin-and-metformin-hydrochloride).

Notes: Table adapted from Table 8 in Endocrine and Metabolic Disorders: Diabetes Mellitus Chapter of Therapeutic Choices. Canadian Pharmacists Association, 2015. All rights reserved. Source: https://www.e-therapeutics.ca/tc.showChapter.action?documentId=c0079#tablc0079n00043. Accessed: July 29, 2015.Other information sources include Product Monograph available from the Health Canada Drug Product Database (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) as well as CADTH 2013 (Updated) Optimal Use Reports on the optimal use of second- and third line therapies for type 2 diabetes mellitus (https://www.cadth.ca/second-third-line-therapies-type-2-diabetes).

Table 2: Injectable medicines: GLP-1 Analogues, Insulin and Insulin Analogues

GLP-1 Analogue Products		Anatomical Therapeutic Chemical (ATC) codes	Dose form(s) & strengths(s)	DDD
Dulaglutide		A10BJ05	Inj 1.5 per 1 ml, 3mg/1ml	0.16 mg
Exenatide		A10BJ01	Inj 250 microg per 1 ml Powder 2 mg	15 ug
Exenatide extended-release		A10BJ01		15 ug
Liraglutide		A10BJ02	Inj 6 microg per 1 ml	1.2 mg
Albiglutide		A10BJ04	Powder 30 mg, 50	5.7 mg
Insulin and Insulin Analogue Products[a]	**Insulin and Insulin Analogue Types**			**DDD**
Insulin aspart	Very rapid-acting insulin analogue	A10AB05	100 unit per 1 ml	40 U
Insulin glulisine	Very rapid-acting insulin analogue	A10AB06	100 unit per 1 ml 200 unit per 1 ml	
Insulin lispro	Very rapid-acting insulin analogue	A10AB04	100 unit per 1 ml 200 unit per 1 ml	
Insulin, regular	Rapid-acting insulin	A10AB01	100 unit per 1 ml	
Insulin, pork	Rapid-acting insulin	A10AB03	100 unit per 1 ml	
Insulin, NPH	Intermediate-acting insulin	A10AC01	100 unit per 1 ml	

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Insulin, pork	Intermediate-acting insulin	A10AC03	100 unit per 1 ml	
Insulin detemir	Long-acting insulin analogue	A10AE05	100 unit per 1 ml	
Insulin glargine	Long-acting insulin analogue	A10AE04	100 unit per 1 ml 300 unit per ml	
Insulin regular/insulin, NPH	Mixed (regular/NPH) human insulin	A10AD01		
Insulin lispro/lispro protamine	Mixed insulin analogue	A10AD04		
Insulin aspart/aspart protamine	Mixed insulin analogue	A10AD05		

DDD = World Health Organization Defined Daily Dose; GLP-1 = glucagon-like peptid-1; NPH = neutral protamine Hagedorn; TZD = thiazolidinedione; U = units.

a All concentrations of insulin and insulin analogue products will be considered, if appropriate (e.g., insulin glargine 100 units/mL and 300 units/mL; insulin lispro 100 units/mL and 200 units/mL). Insulin and insulin analogue products include subsequent entry biologics.
Source of information: Therapeutic Choices. Canadian Pharmacists Association, 2015. [Source: https://www.e-therapeutics.ca/tc.showChapter.action?documentId=c0079#tablc0079n00043 ; Accessed; July 29 2015 (proprietary)]

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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:	Global Action Fund for Fungal Infection, in association with the International Centre for Eye Health, Faculty of Infectious & Tropical Diseases, London School of Hygiene and Tropical Medicine, and The Manchester University.
WHO Technical Department:	N/A
EML / EMLc	EML and EMLc
Section:	Section 21.1 (Ophthalmological preparations) Anti-infective agents
Dose form(s) & strengths(s):	Suspension (eye drops): 5%
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. resubmission, previous EC consideration)	Natamycin eye drops have not previously been considered for inclusion on the EML. Currently, there are no topical antifungals for ophthalmic infections 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, due 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 abrasion 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 the closer one is to the equator (6). An estimated 12 million cases of microbial keratitis occur annually in South East Asia proportion of cases with resultant visual loss or blindness is not known. A statistically significant correlation has been found between Gross National Income (GNI) and aetiology of microbial keratitis. Fungal keratitis is associated with low GNI countries (7). In 2002, a government report from India estimated that keratitis accounted for 9% of cases of blindness in India (8). In Ugandan children with visual impairment, visual loss after corneal ulceration was responsible for nearly 25% of cases (9). The rate of HIV infection in those presenting with fungal keratitis in Tanzania was twice the documented rate in the adult population (10). The annual incidence of microbial keratitis in contact lens wearers varies: 1.2-1,304 /10,000, depending on the type of lens, overnight use and the quality of lens care (11, 12). The proportion of microbial keratitis cases caused by fungi in contact lens wearers varies

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	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 (13-19). 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 (17, 18). These trials had small sample sizes (n=60, n=71) and were therefore likely underpowered to detect 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: RR: 0.99, 95% CI: 0.8 to 1.21 (16). Three trials compared topical natamycin 5% to topical voriconazole 1% and measured best corrected spectacle visual acuity (BCSVA) at 3 months as the primary outcome (13-15). A meta-analysis of these trials performed in a recent Cochrane review suggested that: "there is evidence that natamycin is more effective than voriconazole in the treatment of fungal ulcers" (20). The largest of these three studies, referred to as MUTT1, found quite a substantial benefit from natamycin over voriconazole, particularly for *Fusarium* spp. infections, which are often the majority (15).
Summary of evidence: harms (from the application)	The following adverse events have been identified during post-marketing use of natamycin in clinical practice: 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 (15).
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 (21). The included trials were all conducted out in Asian countries (India, China, Bangladesh) where there is a higher prevalence of fungal keratitis. The authors of this review also concluded natamycin to be a preferable treatment choice, and in particular in the early period of *Fusarium* cases.
WHO Guidelines:	Natamycin 5% eye drops are recommended for treatment of confirmed suppurative keratitis where fungal hyphae are seen on corneal smear in WHO's Regional Office for South-East Asia (SEARO)'s 2004 *Guidelines for the management of corneal ulcer at primary, secondary and tertiary care facilities in the South-East Asia region* (1).
Costs / cost-effectiveness:	The Committee noted the considerable variation in the reported cost of topical natamycin 5% by region as described in the application: Peru US$140, Indonesia US$4 and UK £330 per bottle.
Availability:	Topical natamycin has been used extensively for the treatment of fungal keratitis in South Asia, South-East Asia and North America. It has recently become the standard of care in the UK. It is less widely used in continental Europe or Africa where it is not readily available.
Other considerations:	N/A
Committee Recommendations:	Noting the overall favourable benefit to 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 – deletion - 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 with the addition of language to indicate that the product was not developed nor approved by regulatory authorities for ocular use and of the potential harm to patients resulting from inappropriate handling and storage.
Applicant:	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) & strengths(s):	Injection: 25 mg/mL
Core / Complementary:	Complementary
Individual / Square box listing:	Individual
Background: (if relevant, resubmission eg. 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 the 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 that shows 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 Expert Committee considered that the safe use of bevacizumab (as currently formulated) may require use to be restricted to a single patient per vial, or that any alternative approach would have to comply with safe and sterile injection practices, and appropriate storage conditions, to ensure no 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 Iran, India and Egypt in which some patients experienced ocular adverse 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 WHO Director General, Dr Margaret Chan in 2016. The application referenced United States Pharmacopoeial standards for the manufacturing of intravenous drug formulations and ophthalmic solutions. It states that the manufacturing requirements for intravenous drug formulations allow higher sub-visible particle counts than those for ophthalmic solutions and that therefore bevacizumab is not manufactured to meet 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 as a result of 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. The Expert Committee noted that Nicola Magrini left the room and was not present for the discussion or final recommendation for bevacizumab.
Committee Recommendation:	The Expert Committee did not recommend the deletion of bevacizumab for intravitreal administration for the treatment of neovascular age-related macular degeneration (nAMD). 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 to harms ratio of intravitreal bevacizumab was provided. The Committee reiterated the importance of compounding and administration of intravitreal bevacizumab under sterile conditions.

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Section 22: OXYTOCICS AND ANTIOXYTOCICS

22.1 Oxytocics

Misoprostol – delete indication (PPH prevention) - EML

Misoprostol	**ATC Code: G02AD06**
Proposal:	The application requested deletion of the listed indication of prevention of postpartum haemorrhage (PPH) associated with misoprostol on the EML.
Applicant:	Dr Petra Sevcikova, Professor Allyson Pollock
WHO Technical Department:	The WHO Department of Reproductive Health and Research (RHR), (Maternal and Perinatal Health, Preventing Unsafe Abortion Unit) advised that the evidence presented in the application will be considered at a scoping meeting for updating the PPH guidelines at the end of March 2017. The RHR department did not support any changes to the listing of misoprostol on the EML at this time.
EML / EMLc	EML
Section:	22.1 Oxytocics
Dose form(s) & strengths(s):	Tablet: 200 micrograms
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 this represented a basis to change its previous decision to list. Similarly, in 2015, no new trials were presented comparing misoprostol and oxytocin for prevention of PPH and the Expert Committee saw no reason to draw new conclusions to those made by the 2013 Expert Committee (listed below) and concluded 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)	Haemorrhage has been identified as accounting for over a quarter of maternal deaths, and the leading direct cause of maternal death globally (1). In 2015, the global maternal mortality ratio was estimated to be 216 per 100,000 live births. Reducing maternal mortality to less than 70 per 100,000 live births by 2030 is one of the UN Sustainable Development Goals (SDG 3.1) (2).

Summary of evidence: benefits (from the application)	Compared to the previous application, the current application conducted an updated search for randomized controlled trials 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 versus ergometrine-oxytocin for prevention of PPH (4). Diop et al (3) recorded haemoglobin concentrations pre- and post-delivery in 1,049 women administered 10IU oxytocin IM or 600 mcg misoprostol orally at maternity huts in Senegal. No significant difference in haemoglobin decrease between treatment arms was observed (mean difference (0.3 g/L, 95% CI -8.26 to 8.92, p=0.71). [The authors concluded that both drugs were safe and efficacious when delivered by auxiliary midwives. The authors 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 prophylaxis of PPH]. The application did not report the findings of the systematic review by Tan et al (4).
Summary of evidence: harms (from the application)	Diop et al (3) found both misoprostol and oxytocin to be well tolerated. Shivering was more common among misoprostol-treated patients and nausea more common among oxytocin treated patients. 18 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 by Tan et al (4) in the updated literature search but did not discuss the review's findings. The review included six randomized controlled trials of 4,034 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 PPH (7.6% vs. 4.2%, RR = 1.81, 95%CI: 1.40 to 2.35), and a statistically significantly higher rate of additional uterotonic therapy (19.2% vs. 10.5%, RR = 1.83, 95%CI:1.57 to 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 to 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 option in low-resource settings. Evidence for the comparison of oxytocin versus misoprostol 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 involving over 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 mcg was associated with an increased risk of blood loss greater than 1000 mL compared to oxytocin 10 IU (relative risk (RR) 1.36; 95% confidence interval (CI) 1.17 to 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 to 1.5). With regard to safety, compared to oxytocin, misoprostol was associated with higher rates of shivering (RR 3.3; 95% CI 3.0 to 3.5), diarrhoea (RR 2.52; 95% CI 1.6 to 3.98) and pyrexia C (RR 6.8; 95% CI 5.5 to 8.3).
WHO Guidelines:	The 2012 WHO *Recommendations for the prevention and treatment of postpartum haemorrhage* (5) make the following recommendations for uterotonics in the prevention of PPH: 1. 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) 2. Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH. (Strong recommendation, moderate-quality evidence) 3. 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) 4. 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) ….. 11. 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 (PPH) associated with misoprostol on the EML. The Committee noted that there was very little new clinical data included in the application and that the request was based on a reinterpretation of data previously presented. The Expert Committee acknowledged 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 PPH 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 PPH guidelines are due to be updated in March 2017.

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Section 25: MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

Budesonide + formoterol – addition – EML and 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 (ICS) and a beta-2 agonist bronchodilator.
Applicant:	Professor Jean-William Fitting, Vice-Chair, Adult & Child Lung Health Section, International Union against Tuberculosis and Lung Disease
WHO Technical Department:	WHO Department of Non Communicable Diseases.
EML / EMLc	EML and EMLc
Section:	25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease
Dose form(s) & strengths(s):	EML (adults and adolescents ≥ 12 years): **Dry powder inhaler**: 100 micrograms+6 micrograms per dose; 200 micrograms+6 micrograms per dose EMLc (children 6-11 years): **Dry powder inhaler**: 100 micrograms + 6 micrograms 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, eg. resubmission, previous EC consideration)	Single ingredient inhalers containing budesonide are currently available 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 a rapid onset of action, necessary 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 presently not available for the majority of 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 for 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). Cates et al assessed the combination of formoterol + budesonide as single inhaler therapy against a control group that received inhaled steroids and a separate reliever inhaler in 13 trials involving 13,152 adults including one which involved 224 children less than 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 to 1.44; low quality evidence due to risk of bias and imprecision). Single inhaler therapy significantly reduced the risk of exacerbations requiring treatment of oral corticosteroids (OR 0.83; 95% CI 0.70 to 0.98; moderate quality evidence due to risk of bias). Most trials found a reduction of total ICS dose when using single inhaler therapy. The study including children compared single inhaler therapy with higher dose budesonide. There was a significant reduction in the number of patients with exacerbations needing increased ICS or other treatment among patients using single inhaler therapy (OR 0.33; 95% CI 0.15 to 0.77). Kew et al compared single inhaler therapy with budesonide + formoterol as maintenance and reliever therapy versus higher-dose ICS/LABA combination inhaler maintenance therapy plus SABA reliever in 4 studies involving 9,130 adolescent and adult patients with asthma (4).The number of people who had at least one severe exacerbation requiring hospitalisation or an emergency room visit was significantly lower in the single inhaler therapy group (OR 0.72; 95% CI 0.57 to 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 to 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 will not be 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 2,788 children and adolescents to assess the risk of fatal and non-fatal serious adverse events in people 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 to 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 to 1.27,moderate-quality evidence). Among children, there was weak evidence of moderate quality of an increase in non-fatal serious adverse events in children in the formoterol + ICS group (OR 1.62, 95%CI 0.80 to 3.28). Asthma-related serious events were lower in the formoterol + ICS arm among adults (OR 0.49, 95% CI0.28 to 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 to 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. The Global Initiative for Asthma (GINA) *Global Strategy for Asthma Management and Prevention* recommends 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 state that efficacy studies have shown that there is no difference in efficacy giving ICS and LABA in combination or separately in circumstances where there is good adherence. The guidelines recommend that patients taking budesonide + formoterol

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	as rescue/reliever therapy at least daily on a regular basis should be reviewed (8).
Costs / cost-effectiveness:	The application estimates the annual UK treatment costs for low-dose budesonide + formoterol to be US$ 265 to US$ 335, and high-dose treatment to be US$ 528 to US$ 669. Two studies assessed the cost-effectiveness of the budesonide +formoterol versus ICS alone (9, 10). In both studies patients receiving budesonide + formoterol therapy had more symptom-free days and less exacerbation events than patients with budesonide or fluticasone alone. In the first study the budesonide + formoterol therapy had slighter cost versus ICS alone. The incremental cost-effectiveness ration (ICER) was 2.32 Euros (US$ 2.62) per symptom-free day gained (9). In the second study the budesonide + formoterol therapy was dominant (more effective and less costly: 80 Euros or US$ 90 less per patient over 12 weeks)(10). Also cost-effectiveness of the single inhaler therapy was assessed in other several studies versus either a higher dosage ICS plus SABA reliever therapy, or a similar ICS/LABA therapy plus SABA or LABA reliever therapy, or a higher dosage ICS/LABA therapy plus SABA reliever therapy. In most comparisons, the budesonide + formoterol single inhaler therapy was more effective at a lower total cost, and was thus dominant (11).
Availability:	AstraZeneca (Symbicort Turbuhaler®) TEVA Pharma B.V (DuoResp Spiromax®)
Other considerations:	Current British guidelines recommend the single inhaler therapy at steps 2-3 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 to control the disease "maintenance therapy" for patients that 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 bronchodilator 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) – addition - EMLc

Ready-to-use therapeutic food (RUTF)	**ATC code: n/a**
Proposal:	Addition of 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:	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: Solutions Correcting Water, Electrolyte and Acid-based Disturbances, 26.3 Miscellaneous.
Dose form(s) & strengths(s):	Lipid-based paste for oral consumption Nutritional composition per 100 g:

Energy:	520-550 kcal
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):	0.8-1.2mg
Vitamin D (cholecalciferol):	15-20 mcg
Vitamin C (ascorbic acid):	50 mg minimum
Vitamin E (tocopherol):	20 mg minimum
Vitamin K (phytonadione):	15-30 mcg
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 mcg minimum
Vitamin B9 (folic acid):	200 mcg minimum
Vitamin B3 (niacin):	5 mg minimum
Vitamin B5 (pantotenic acid):	3 mg minimum
Vitamin B7 (biotin):	60 mcg minimum
Sodium:	290 mg maximum
Potassium:	1100-1400 mg
Calcium:	300-600 mg
Phosphorous:	300-600 mg
Magnesium:	80-140 mg
Iron:	10-14 mg
Zinc:	11-14 mg
Copper:	1.4-1.8 mg
Selenium:	20-40 mcg
Iodine:	70-140 mcg

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Core / Complementary:	Core
Individual / Square box listing:	Individual
Background: (if relevant, eg. 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 over 17 million children are affected by SAM globally, while less than 20% of affected children accessed 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 from 6-59 months of age: A 2013 Cochrane systematic review and meta-analysis by Schoonees et al. 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% CI 1.16 to 1.50). The evidence was considered to be 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 by Lenters et al. of treatment of severe and moderate acute malnutrition compared children who received RUTF with those who received standard care (in-patient treatment followed by provision of corn soy blend (CSB) food for feeding at home). The evidence was also graded as low-quality and limited (largely the same studies included in the Cochrane Review). Results found that children given RUTF for the community-based treatment of SAM were 51% more likely to achieve nutritional recovery than the standard care group (RR: 1.51; 95% CI 1.04 to 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). Due to the limited high quality comparative trials evaluating community-based treatment using RUTF, Lenters et al. complemented the 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 case fatality rate to be at 4% (range: 2-7%), and a recovery rate of 80% (range: 50-93%). Overall, the review argued that the community-based management of uncomplicated SAM in children 6-59 months of age 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 12-15g protein) were 10 times more likely to recover (odds ratio (OR) 10.28; 95% CI1.02-104.95) (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 UNICEF Supply Division had less than 5 ppb aflatoxin. Schoonees et al. found no difference in mortality between children who received RUTF and those who received standard diets (RR 0.97; 95% CI 0.46 – 2.05; n = 599). Similarly, there was 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 Alimentarius (CCNFSDU) is currently undergoing the process of developing guidelines for RUTF.

WHO Guidelines:	The proposed formulation and nutritional composition is consistent with the nutritional composition of RUTF recommended in in the joint statement on community-based management of severe acute malnutrition (6). Therapeutic feeding approaches involving RUTF in the management of SAM in children 6-59 months old 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 programs. In the published literature, the cost of RUTF product per child treated ranged from US$ 39.6-104.65 (8-13). In addition to cost-effectiveness per child treated, a small number of studies also included analysis of cost per disutility adjusted life-year (DALY) or life saved. The Malawi and Zambia studies estimated cost-effectiveness to be US$ 42-53 per DALY or US$ 1,365-1,760 per life saved (9, 10). A recent cost-effectiveness analysis of a large-scale program in Nigeria found US$30 per DALY and US$ 1117 per life saved. As noted in the WHO Guideline 2013 Update, no cost data is available to compare the cost of treatment using F-100 therapeutic food product with RUTF [3].
Availability:	Currently RUTF is provided by UNICEF for specific nutrition programs. RUTF 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 (SAM) in children of 6-59 months of age and its alignment with WHO Guideline: Updates on the management of SAM in Infants and Children (2013). The Committee agreed that it is necessary to improve the access to RUTF in health facilities at country level for the outpatient treatment of SAM. However, the Committee considered that listing of RUTF on the EML may have potential implications on the availability of alternative products or formulations. Their inclusion in the EML might carry in some countries and manufacturing sites potential implications to comply with requirements for pharmaceutical products and potentially have an impact on cost and access. Therefore, the Committee did not recommend the addition of RUTF to the EMLc. The Committee recommended the need for further analysis of the implications and impacts of including RUTF in the EMLc and requested 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 capability to comply with the requirements by local and international producers. -Cost and access if a medicine/pharmaceutical vs a food. -Appropriate use of RUTF, i.e. only for uncomplicated cases of SAM and not for other children. -Advances of the Codex Committee for Special Dietary Uses on the RUTF guideline development -Outcome of ongoing systematic reviews on effectiveness and safety of RUTF.

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