EML Secretariat proposal for changes to listings and reviews of medicines on the Model List of Essential Medicines for Children (EMLc)

Proposal:

The Expert Committee is requested to consider proposed amendments to listings and proposed reviews of essential medicines for children on the EMLc.

Background:

In collaboration with the Secretariat of the Global Accelerator for Paediatric Formulations (GAP-f), the EML Secretariat has carried out a review of the age-appropriateness of formulations of medicines listed on the EMLc.

The review project included the following activities:

1. *Paediatric formulations assessment*
    - Identification of formulations of essential medicines that could be proposed for potential addition to the EMLc given their therapeutic utility in children, as well as identification of formulations to be proposed for deletion from the EMLc because they are not appropriate or are not available.
    - Identification of formulation gaps in essential medicines for children to inform GAP-f research and development activities to fill priority unmet formulation needs for the paediatric population.
2. *EML / EMLc comparison*
    - A systematic comparison of medicines and indications listed on the EML and EMLc to identify medicines on the EML that have potential therapeutic utility in children but that are not currently included on the EMLc.

Review methodology and findings:

The methodology and findings for the paediatric formulations assessment are described in Attachment 1 – *"Report of a comprehensive review of the age-appropriateness of formulations listed on the WHO EMLc".*

The methodology and findings for the EML / EMLc comparison are described in Attachment 2 – "*Summary Report on the review of the EML to identify medicines that have potential therapeutic utility in children but are not included on the EMLc"*

Proposed actions for Expert Committee consideration:

Following this review, the findings were discussed with international experts, and other relevant stakeholders to finalize proposed actions for Expert Committee consideration. A summary of the proposed amendments and reviews for Expert Committee consideration is presented in Annex 1:

1. Proposed changes to EMLc listings arising from the review of age-appropriateness of formulations (Annex 1, Table 1)
2. Proposed changes to the EMLc arising from the comparison report of EML versus EMLc (Annex 1, Table 2)
3. Proposals for review of medicines / therapeutic areas arising from the comparison report of EML versus EMLc (Annex 1, Table 3).

Attachments:

1. Report of a comprehensive review of the age-appropriateness of formulations listed on the WHO EMLc
    a. Annex A: Summary report of survey results, identifying the reasons for the missing formulations and elements of context and rationale for prioritization of products missing but deemed critical.
    b. Annex B: Summary report of an evaluation of usage for oral child-appropriate formulations (CAFs) on the Model List of Essential Medicines for Children.
2. Summary report on the review of the EML to identify medicines that have potential therapeutic utility in children but are not included on the EMLc.

Annex 1: Amendments and reviews of essential medicines for children on the EMLc proposed by the Secretariat

Table 1 – EML Secretariat proposed changes to EMLc listings following review of age-appropriateness of formulations.

Section	Medicine	Indication	Add new formulation/strength	Delete existing formulation/strength	Other changes
2.1	Ibuprofen	Analgesia	Oral liquid: 100 mg/5 mL		
2.1	Paracetamol	Analgesia	Oral liquid: 250 mg/5 mL Suppository: 250 mg Tablet (dispersible): 100 mg, 250 mg	Tablet: 100 mg	Include alternative medicine name "(acetaminophen)" in listing Replace Tablet: 100 mg to 500 mg with Tablet: 250 mg, 325 mg, 500 mg Add note: "The presence of both 120 mg/5 mL and 125 mg/5mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided."
5	Carbamazepine	Epilepsy or seizures	Tablet (scored) 400 mg		
5	Diazepam	Status epilepticus			Modify existing listing as follows: Rectal solution: 2 mg/mL in 1.25 mL and 2.5 mL; 4 mg/mL in 2.5 mL rectal tubes Rectal gel: 5 mg/mL in 0.5 mL, 2 mL and 4 mL rectal delivery systems
5	Midazolam	Status epilepticus		Ampoule: 10 mg/mL	Include information of volume of pre-filled oral syringes (oromucosal solution) and vials (solution for injection for buccal administration)
5	Phenobarbital	Epilepsy or seizures Status epilepticus	Injection: 30 mg/mL or 60 mg/mL (sodium).		

5	Phenytoin	Epilepsy or seizures		Oral liquid: 25 mg/5 mL (phenytoin)	Specify phenytoin sodium or phenytoin (free acid form) for all formulations Remove vial size for phenytoin 50 mg/mL (phenytoin sodium) injection Remove note regarding presence of both oral liquid strengths on the same market
5	Valproic aid (sodium valproate)	Status epilepticus	Injection: 100 mg/mL in 3 mL ampoule		
6.1.1	Ivermectin	Intestinal helminth infections			Remove reference to ivermectin 3 mg tablets being scored
6.1.1	Levamisole	Intestinal helminth infections		Tablet: 150 mg (as hydrochloride)	
6.1.1	Praziquantel	Intestinal helminth infections	Tablet: 500 mg		Specify praziquantel 600 mg tablets being scored
6.1.1	Pyrantel	Intestinal helminth infections		Oral liquid: 50 mg/mL (as embonate or pamoate)	
6.1.2	Ivermectin	Filarial infections			Remove reference to ivermectin 3 mg tablets being scored
6.1.3	Praziquantel	Schistosomal infections	Tablet: 500 mg		Specify praziquantel 600 mg tablets being scored
6.1.3	Triclabendazole	Trematode infections			Specify triclabendazole 250 mg tablets being scored
6.1.4	Albendazole	Echinococcosis and cysticercosis	Tablet (chewable): 200 mg		Specify albendazole 400 mg chewable tablets as scored
6.1.4	Mebendazole	Echinococcosis and cysticercosis	Tablet (chewable): 100 mg		
6.1.4	Praziquantel	Echinococcosis and cysticercosis	Tablet: 150 mg		Specify praziquantel 600 mg tablets being scored
6.2.1	Amikacin	Bacterial infections (various)	Injection: 50 mg/mL (as sulfate) in 2 mL vial		

6.2.1	Amoxicillin	Bacterial infections (various)	Tablet (dispersible, scored): 250 mg, 500 mg (as trihydrate)		
6.2.1	Amoxicillin + clavulanic acid	Bacterial infections (various)	Tablet (dispersible): 250 mg (as trihydrate) + 62.5 mg (as potassium salt		
6.2.1	Cefalexin	Bacterial infections (various)bacterial infections (various)	Tablet (dispersible): 125 mg;, 250 mg		
6.2.1	Chloramphenicol	Bacterial meningitis		Capsule: 250 mg Oral liquid: 150 mg/5mL (as palmitate)	
6.2.1	Clindamycin	Bone and joint infections necrotizing fasciitis	Powder for oral liquid: 75 mg/5 mL (as palmitate hydrochloride)	Oral liquid: 75 mg/5mL (as palmitate)	
6.2.1	Cloxacillin (and therapeutic alternatives)	Bone and joint infections Skin and soft tissue infections Sepsis	Capsule: 250 mg Powder for injection: 250 mg (as sodium) in vial Powder for oral liquid: 250 mg/5 mL (as sodium)		
6.2.1	Doxycycline	Cholera Community-acquired pneumonia	Powder for oral liquid: 25 mg/5 mL (monohydrate) Oral liquid: 50 mg/5 mL (calcium) Tablet (dispersible): 100 mg (as monohydrate	Oral liquid: 25 mg/5 mL (anhydrous)	
6.2.1	Metronidazole	Bacterial infections (various)			Replace strength range for metronidazole tablet with specific strengths: 200 mg, 250 mg, 400 mg, 500 mg
6.2.1	Nitrofurantoin	Lower urinary tract infections	Solid oral dosage form: 50 mg		Replace 'tablet' with 'solid oral dosage form'
6.2.1	Phenoxymethylpenicillin	Bacterial infections (various)			Replace 'tablet' with 'solid oral dosage form'
6.2.1	Sulfamethoxazole + trimethoprim	Lower urinary tract infections Acute invasive bacterial diarrhoea / dysentery	Tablet (dispersible): 100 mg + 20 mg		

6.2.2	Azithromycin	Bacterial infections (various)	Powder for oral liquid: 200 mg/5 mL (anhydrous)	Oral liquid: 200 mg /5 mL	Replace 'capsule' with 'solid oral dosage form'
6.2.2	Cefixime	Acute invasive bacterial diarrhoea / dysentery	Solid oral dosage form: 200 mg, 400 mg (as trihydrate)	Tablet: 200 mg (as trihydrate)	
6.2.2	Cefotaxime	Bacterial infections (various)	Powder for injection: 500 mg, 1 g, 2 g (as sodium) in vial		
6.2.2	Ceftriaxone	Bacterial infections (various)	Powder for injection: 500 mg (as sodium) in vial		
6.2.2	Ciprofloxacin	Bacterial infections (various)	Solid oral dosage form: 100 mg (as hydrochloride)		
6.2.2	Clarithromycin	Pharyngitis	Solid oral dosage form: 250 mg	Solid oral dosage form: 500 mg	
6.2.2	Vancomycin (oral)	*C. difficile* infection			Add note to indicate that vancomycin powder for injection may also be used for oral administration
6.2.2	Vancomycin (iv)	Endophthalmitis Necrotizing fasciitis High-risk febrile neutropenia	Powder for injection: 500 mg, 1 g (as hydrochloride) in vial		
6.2.3	Colistin	Infections due to multidrug-resistant organisms			Include equivalent strength in colistin base activity: "(equivalent to 34 mg colisting base activity)"
6.2.3	Linezolid	Infections due to multidrug-resistant organisms	Tablet (dispersible): 150 mg	Tablet: 400 mg, 600 mg	
6.2.3	Polymyxin B	Infections due to multidrug-resistant organisms			Include equivalent strength in mg of polymyxin B base: "(equivalent to 50 mg polymyxin B base)"
6.2.4	Clofazimine	Leprosy			Change description from 'capsule' to 'solid oral dosage form'
6.2.4	Rifampicin	Leprosy	Oral liquid: 20 mg/mL		

6.3	Amphotericin B	Invasive fungal infections			Modify existing listing as follows: Powder for injection: 50 mg in vial (liposomal complex)* Powder for injection: 50 mg in vial (as sodium deoxycholate) *Liposomal amphotericin B has a better safety profile than the deoxycholate formulation and should be prioritized for seletion and use depending on local availability and cost
6.3	Fluconazole	Invasive fungal infections	Powder for oral liquid: 50 mg/5 mL		
6.3	Nystatin	*Candida* infections		Oral liquid: 50 mg/5 mL Tablet: 100 000 IU	Change description from 'tablet' to 'solid oral dosage form'
6.5.1	Metronidazole	Amoebiasis			Replace strength range for metronidazole tablet with specific strengths: 200 mg, 250 mg, 400 mg, 500 mg
6.5.2	Amphotericin b	Leishmaniasis			Modify existing listing as follows: Powder for injection: 50 mg in vial (liposomal complex)* Powder for injection: 50 mg in vial (as sodium deoxycholate) *Liposomal amphotericin B has a better safety profile than the deoxycholate formulation and should be prioritized for seletion and use depending on local availability and cost

6.5.2	Sodium stibogluconate or meglumine antimoniate	Leishmaniasis			List each medicine separately as follows: Sodium stibogluconate Injection: 100 mg/mL in 30 mL vial Meglumine antimoniate Injection: 1.5 g/5 mL in 5 mL ampoule
6.5.5.1	Pentamidine	African trypanosomiasis	Powder for injection: 300 mg (as isethionate) in vial	Powder for injection: 200 mg (as isethionate) in vial	
6.5.5.1	Eflornithine	African trypanosomiasis			Update bottle size from 100 mL to 50 mL
6.5.5.1	Nifurtimox	African trypanosomiasis	Tablet (scored): 30 mg		Specify nifurtimox 120 mg tablets being scored
6.5.5.2	Benznidazole	American trypanosomiasis			Specify benznidazole 50 mg and 100 mg tablets being scored
6.5.5.2	Nifurtimox	American trypanosomiasis		Tablet: 250 mg	Specify nifurtimox 30 mg and 120 mg tablets being scored
6.6	Ivermectin	Scabies infection			Remove reference to ivermectin 3 mg tablets being scored
7.1	Ibuprofen	Migraine	Oral liquid: 100 mg/5 mL		
7.1	Paracetamol	Migraine	Oral liquid: 250 mg/5 mL Suppository: 250 mg Tablet (dispersible): 100 mg, 250 mg	Tablet: 100 mg	Include alternative medicine name of acetaminophen in listing Replace Tablet: 100 mg to 500 mg with Tablet: 250 mg, 325 mg, 500 mg Add note: "The presence of both 120 mg/5 mL and 125 mg/5mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.

8.1	Adalimumab	Crohn disease Juvenile idiopathic arthritis Ankylosing spondylitis Rheumatoid arthritis	Injection: 20 mg/0.4 mL, 10 mg/0.2 mL		
8.1	Azathioprine	Organ transplant rejection	Tablet: 25 mg Oral liquid: 10 mg/mL Powder for injection: 50 mg (as sodium salt) in vial		
8.1	Ciclosporin	Organ transplant rejection	Oral solution: 100 mg/mL		
8.2.1	Arsenic trioxide	Acute promyelocytic leukaemia	Concentrate for solution for infusion: 2 mg/mL		
8.2.1	Bleomycin	Hodgkin lymphoma Kaposi sarcoma Ovarian & testicular germ cell tumours			Change description of product strength from 15 mg to 15 000 IU
8.2.1	Calcium folinate	Burkitt lymphoma Osteosarcoma	Injection: 7.5 mg/mL in 2 mL ampoule, 10 mg/mL in 5 mL ampoule		Include alternative medicine name "(leucovorin calcium)" in listing
8.2.1	Cyclophosphamide	Acute lymphoblastic leukaemia Burkitt lymphoma Diffuse large B-cell lymphoma Ewing sarcoma Hodgkin lymphoma Low-grade glioma Nephroblastoma Rhabdomyosarcoma			Change description from 'tablet' to 'solid oral dosage form'

8.2.1	Cytarabine	Acute lymphoblastic leukaemia Acute myeloid leukaemia Acute promyelocytic leukaemia Burkitt lymphoma	Solution for injection: 100 mg/mL in vial		
8.2.1	Dacarbazine	Hodgkin lymphoma Kaposi sarcoma Ovarian & testicular germ cell tumours	Powder for injection: 200 mg in vial		
8.2.1	Daunorubicin	Acute lymphoblastic leukaemia Acute promyelocytic leukaemia	Powder for injection: 20 mg in vial Injection: 2 mg/mL, 5 mg/mL		
8.2.1	Doxorubicin	Acute lymphoblastic leukaemia Burkitt lymphoma Diffuse large B-cell lymphoma Ewing sarcoma Hodgkin lymphoma Kaposi sarcoma Nephroblastoma Osteosarcoma	Injection: 2 mg/mL (hydrochloride) in vial		

8.2.1	Etoposide	Acute lymphoblastic leukaemia Acute myeloid leukaemia Burkitt lymphoma Ewing sarcoma Hodgkin lymphoma Nephroblastoma Osteosarcoma Ovarian & testicular germ cell tumours Retinoblastoma	Powder for injection: 100 mg (as phosphate) in vial		
8.2.1	Fluorouracil	Early stage colon cancer Early stage rectal cancer Metastatic colorectal cancer Nasopharyngeal cancer			Remove specification of vial size
8.2.1	Hydroxycarbamide	Chronic myeloid leukaemia	Solid oral dosage form: 100 mg	Solid oral dosage form: 250 mg	Include alternative medicine name "(hydroxyurea)" in listing
8.2.1	Mercaptopurine	Acute lymphoblastic leukaemia Acute promyelocytic leukaemia	Oral liquid: 20 mg/mL		
8.2.1	Methotrexate	Acute lymphoblastic leukaemia Acute promyelocytic leukaemia Burkitt lymphoma Osteosarcoma	Injection: 50 mg/2 mL in vial Concentrated injection: 1000 mg/10 mL in vial		
8.2.1	Pegaspargase	Acute lymphoblastic leukaemia	Powder for injection: 3,750 units in vial		
8.2.1	Vinorelbine	Rhabdomyosarcoma		Capsule: 80 mg	Simplify description of injection formulation to 10 mg/mL in 1 mL or 5 mL vial

8.2.2	Dasatinib	Imatinib-resistant chronic myeloid leukaemia		Tablet 100 mg, 140 mg	
12.3	Enalapril	Hypertension	Oral solution: 1 mg/mL (as hydrogen maleate) Tablet: 10 mg (as hydrogen maleate)		
12.4	Digoxin	Heart failure	Injection: 100 micrograms/mL in 1 mL ampoule Tablet: 125 micrograms		Transfer listing from the core to the complementary list
12.4	Furosemide	Heart failure	Injection: 10 mg/mL in 5 mL ampoule Oral liquid: 50 mg/5 mL Tablet: 20 mg		
16	Furosemide	Diuresis	Injection: 10 mg/mL in 5 mL ampoule Oral liquid: 50 mg/5 mL Tablet: 20 mg	Tablet: 10 mg	

Table 2 – EML Secretariat proposed changes to EMLc following arising from the comparison report of EML versus EMLc

Section	Medicine	Indication	EMLc history/background	Secretariat proposal
13.1	Seleniuim sulfide	Seborrhoeic dermatitis Pityriasis versicolor	Selenium sulfide was recommended for inclusion and listed on the complimentary list of the first EMLc in 2007. In 2011, the listing was recommended to be moved from the complementary to the core list. However, it appears to have been inadvertently omitted from the list from this time onwards.	Reinstate the listing for seleniuim sulfide detergent-based suspension 2% on the core list of the EMLc
20	Atracurium	Neuromuscular blockade	In 2007, the first EMLc included vecuronium with a square box, mentioning atracurium as an alternative.	Vecuronium and atracurium are both non-depolarizing neuromuscular blocking agents. They have the same mechanism of action, and a similar duration of action (intermediate-acting) Both are approved for use in infants and children. Propose to include atracurium as a therapeutic alternative under the square box listing for vecuronium on the EMLc.

Table 3 – EML Secretariat proposals for review of medicines / therapeutic areas arising from the comparison report of EML versus EMLc

Section	Medicine(s)	Indication	EMLc background	Secretariat proposal
1.2	Ephedrine	Prevention of hypotension during spinal anaesthesia	In 2007, the Expert Committee recommended that ephedrine should not be included on the EMLc. It is only listed on the EML for use in spinal anaesthesia during delivery, to prevent hypotension.	A review of the public health relevance and evidence for the use of ephedrine for hypotension secondary to spinal anaesthesia in children could be considered.
2.2	Fentanyl (transdermal)	Chronic cancer pain	In 2017, when transdermal fentanyl was added to the EML, the Expert Committee did not recommend inclusion on the EMLc because of adverse effects and concerns regarding overdosing.	An updated review of the evidence for use of transdermal fentanyl in children with chronic cancer pain could be considered.
4.2	Methylthioninium chloride (methylene blue)	Acquired methaemoglobinaemia	In 2007, the Subcommittee noted that the reviewers questioned the comparative effectiveness and safety of methylthioninum chloride versus sodium nitrite for the treatment of methaemoglobinemia and therefore recommended that neither be endorsed as essential at this time without further review.	An updated review of the public health relevance and evidence for medicines for the management of acquired methaemoglobinaemia in children could be considered.
4.2	Sodium nitrite Sodium thiosulfate	Cyanide poisoning	n 2007 the Expert Committee did not recommend inclusion of sodium nitrite or sodium thiosulphate for use in cyanide poisoning, noting that the clinical need for medicines for cyanide poisoning in children was not clear. The Committee recommended the public health relevance of these products be clarified.	A review of the public health need for antidotes for cyanide poisoning in children could be considered
6.2.2	Clarithromycin	Community acquired pneumonia Eradication of *H. pylori*	Clarithromycin is currently included on the EMLc only as a second-choice treatment option for bacterial pharyngitis.	A review of the public health relevance and evidence for eradication of *H. pylori* infection in children could be considered. Clarithromycin is not currently recommended for the treatment of community- or hospital-acquired bacterial pneumonia in children in the EMLc, the EML AWaRe antibiotic book, nor in the WHO Recommendations for management of common childhood conditions (2012).

8.1	Golimumab	Juvenile idiopathic arthritis	In 2019, the Expert Committee recommended the addition of adalimumab with a square box to the complementary list of the EML and EMLc for the second-line treatment of severe chronic inflammatory autoimmune disorders (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease) on the basis of the positive benefit to harm profile of these medicines. For adult patients, therapeutically equivalent alternatives to adalimumab are limited to etanercept, infliximab, certolizumab pegol and golimumab. For children, therapeutically equivalent alternatives should be limited to etanercept and infliximab (based on available evidence).	An updated review of the evidence for use of golimumab in children with JIA could be considered.
8.2.1	Paclitaxel Vinblastine	Kaposi sarcoma	Paclitaxel and vinblastine have not previously been considered for the treatment of Kaposi sarcoma in children. In 2019, the indication of Kaposi sarcoma was included in the EMLc listings for bleomycin, doxorubicin and vincristine. Paclitaxel and vinblastine were not proposed nor reviewed at that time.	A review of the evidence for paclitaxel and vinorelbine for treatment of Kaposi sarcoma in children could be considered.
10.2	Tranexamic acid	Haemorrhage associated with trauma	Tranexamic acid has not been previously considered for use in children with haemorrhage associated with trauma	A review of the available evidence for tranexamic acid for the treatment of children with haemorrhage associated with trauma (and other indications?) could be considered.
12.2	Digoxin Lidocaine Verapamil	Cardiac arrythmias	In 2007, the EMLc Subcommittee considered that without having detailed evidence of the efficacy and safety of antiarrhythmic medicines in children, it could not endorse any for inclusion on the EMLc.	A review of the public health relevance and evidence for medicines for the management of cardiac arrythmias in children could be considered.
12.3	Amlodipine Hydrochlorothiazide Losartan	Hypertension	In 2007, the EMLc Subcommittee considered that without having detailed evidence of the efficacy and safety of antihypertensive medicines in children, it could not endorse any for inclusion on the EMLc.	A review of the public health relevance and evidence for medicines for the management of hypertension in children could be considered.

12.3	Sodium nitroprusside	Hypertensive crisis	In 2007, the EMLc Subcommittee considered that without having detailed evidence of the efficacy and safety of antihypertensive medicines in children, it could not endorse any for inclusion on the EMLc.	A review of the public health relevance and evidence for medicines for the management of hypertensive crisis in children could be considered.
12.6	HMG Co-A reductase inhibitors	Hyperlipidaemia Heterozygous familial hypercholesterolaemia	In 2013, the Expert Committee did not recommend inclusion of statins on the EMLc for use in children, considering that the indications for statin use in children were rare and that the long-term risks and benefits had not been well established. However, given the global prevalence of obesity, including in children, the Committee recommended that a "watching brief" be maintained on this topic. Not only will the public health relevance need to be considered, but emerging evidence on the choice of an appropriate approach to lowering very lipid levels in children would need to be informed by sufficiently good evidence.	A review of the public health relevance and evidence for the use of statins in children is proposed, in particular for the indication of heterozygous familial hypercholesterolaemia.
14.2	Amidotriozate	Diagnostic agent	In 2007, the Expert Committee recommended inclusion of barium sulfate on the EMLc but considered that an expert review of radiocontrast imaging of children should be undertaken before listing other radiocontrast media	A review of the public health relevance and evidence for the use of iodinated radiocontrast media in children could be considered.
17.3	Mesalazine Sulfasalazine	Ulcerative colitis	In 2007, the EMLc Subcommittee that GI anti-inflammatory medicines should not be included on the EMLc on epidemiological grounds.	An updated review of the public health relevance and evidence for medicines for the management of ulcerative colitis could be considered.
21.4	Latanoprost Pilocarpine Timolol	Glaucoma	In 2007, the Expert Committee considered that glaucoma was rare in children and did not include medicines for the treatment of glaucoma in the EMLc.	A review of the public health relevance of glaucoma in children and evidence for medicines for the treatment of children could be considered.
25.1	Budesonide + formoterol	Asthma	In 2017, when budesonide + eformoterol was added to the EML, the Expert Committee did not recommend inclusion on the EMLc because of safety concerns about high doses of inhaled corticosteroids in children.	An updated review of the evidence for use of budesonide + formoterol in children with asthma could be considered.

27	Calcium	Calcium deficiency	In 2013, following consideration of an application requesting addition of calcium to the EML for calcium supplementation in pregnant women, the Expert Committee indicated that an application for calcium and other micronutrient supplementation in children would be required before these products could be considered for addition to the EMLc.	A review of the public health relevance and evidence for the use of calcium as a nutritional supplement in children could be considered.