M E M O R A N D U M

From:	Director MSD	**To:**	Director HPS	**Date:**	06/11/2024
Our ref:		**Attention:**	Secretary of the WHO Expert Committee on Selection and Use of Essential Medicines		
Your ref:		**Through:**			
Originator:	Tarun DUA/MSD/BRH	**Subject:**	***PROPOSAL FOR CHANGES TO THE SECTION ON "MEDICINES FOR DISEASES AFFECTING THE NERVOUS SYSTEM" OF THE WHO MODEL LIST OF ESSENTIAL MEDICINES***		

The Department of Mental Health, Brain Health and Substance use requests the Expert Committee on Selection and Use of Essential Medicines to consider the changes to the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) as per the proposal and rationale provided below.

The proposal

1. Rename section 5. "Medicines for diseases of the nervous system" to "Medicines for neurological disorders" (See Annex for the mock-up)

2. Relocate the current section 7 "anti-migraine medicines" to section 5 "Medicines for neurological disorders".

3. Add a new section entitled "Medicines for brain infections" within section 5.

3a. Add in this section a new sub-section entitled "Viral brain infections" and duplicate the current listing for aciclovir and valaciclovir currently listed in sub-section "6.4 Antiviral medicines", without changes to the current specifications or removing it from section 6.4.

3b. In the above section on "Medicines for brain infections", add a new sub-section entitled "Bacterial brain infections" and duplicate the current listings for amoxicillin, ampicillin, benzylpenicillin, cefotaxime, ceftriaxone, chloramphenicol, gentamicin and meropenem in sub-sections 6.2.1 "Access group antibiotics" and 6.2.2 "Watch group antibiotics" "Antibacterials" without changes to the current specifications or removing them from section 6.2.1 and 6.2.2.

4. Add a new section entitled "Medicines for disorders of the peripheral nervous system".

4a. Duplicate in this section the current listing for "normal immunoglobulin" currently listed in sub-section 11.2. "Blood and blood components" with the indication solely for Guillain-Barré syndrome and the intravenous formulation, without removing it from section 11.2.

4b. In the above section, duplicate the current listing for neostigmine and pyridostigmine, currently listed in section 20 "Muscle relaxants (peripherally-acting) and cholinesterase inhibitors" with an indication for myasthenia gravis, without changes to the current specifications or removing it from section 20.

5. Replace the current "*" observation message for valproic acid (sodium valproate) regarding its harmful effects in women and girls of child-bearing potential in line with the new guidance provided by the WHO mhGAP guidelines as follows: "*Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb"*

6. In addition to the above, the department will be submitting applications on medicines for infantile spasm and trigeminal neuralgia for their inclusion in the section 5 on "medicines for neurological disorders".

Rationale for the above proposal

The rationale for the modification to the name of section 5 'neurological disorders' is grounded on the need to acknowledge the impact and the need to appropriately represent disorders that are not commonly classified or referred to as diseases. Such change is also in line with the terminology used in the Intersectoral global action plan for epilepsy and other *neurological disorders*[1].

Since migraine is a neurological disorder, we are therefore proposing to relocate section 7 "antimigraine medicines" to section 5 to ensure that medicines for all neurological disorders are situated in its appropriate and one section.

A new section for medicines for brain infections is being proposed to appropriately represent the essential medications used to treat viral and bacterial infections of the brain. Aciclovir was added in 1997 on the EML with an indication for herpes simplex infections (TRS 882), the application included herpesviral encephalitis as a use case for the evidence presented: "*Intravenous and oral preparations of aciclovir are included since they are used in disseminated herpes simplex and disseminated herpes zoster infections in immunocomprised patients and in herpesviral encephalitis". Likewise,* Valaciclovir (as therapeutic alternative), is equally already included on the WHO Model List and recent WHO technical guidance highlights that: *"Where IV aciclovir is not available, oral valaciclovir may be preferable to oral aciclovir or nothing, because it has relatively good bioavailability and penetration into the CNS"*[2] . Moreover, amoxicillin, ampicillin, benzylpenicillin, cefotaxime, ceftriaxone, chloramphenicol, gentamicin and meropenem, are currently listed on the EML but under general sections 6.2.1 and 6.2.2. With the listing of medicines that are already part of the WHO Model List, with a specific indication for treatment of bacterial brain infections, awareness of the condition will be raised, and appropriate guidance will be provided to countries on the essential medicines that should be accessible to treat this condition.

The rationale for the request to create a new section for disorders of the peripheral nervous system is to represent these categories of neurological disorders in the appropriate section of the EML. Guillain-Barré syndrome is a neuro-immunological condition that affects the peripheral nervous system, and most cases follow an infection due to a virus or bacteria. Guillain-Barré syndrome often accompanies epidemic infections such as Zika virus infection[3]. The syndrome requires urgent medical care, and a medicine used for its treatment is already included on WHO Model List but without a specific population or disease being mentioned. This is despite the fact that normal human immunoglobulin was reinstated on the EML in 2007 with an indication of use in Guillain-Barré syndrome (TRS 946): "*The Committee therefore agreed to list polyvalent human immunoglobulins on the complementary list in Section 11.2, Plasma fractions for specific use, in the following forms: — human normal immunoglobulin for intramuscular administration: 16% protein solution; and — human normal immunoglobulin for intravenous administration: 5%, 10% protein solution. However, the Committee noted that unless the prices of the products were substantially reduced, access in developing countries would remain a problem. Countries are advised to acquire human immunoglobulins for specific disorders, such as primary immunodeficiency,* ***Guillain-Barré syndrome*** *and Kawasaki disease*". Thus the appropriate representation of this medicine on the WHO Model List has the potential to support several actions that may lead to decreased prices and better access and provide guidance to countries to improve the selection of essential medicines. We note that the section refers solely to Guillain-Barré syndrome and as such, other indications currently on the Model list should not be duplicated

(i.e. primary immunodeficiency, Kawasaki disease and Langerhans histiocytosis). Moreover, considering that only intravenous formulations are the standard of care for Guillain-Barré syndrome, the currently listed intramuscular and subcutaneous formulations should not be duplicated.

Pyridostigmine and neostigmine have been first included on the WHO Model List (since 1977) and WHO Model List for Children (since 2007) with the indication for use in myasthenia gravis. However, both medicines are currently listed in section 20 without an indication for myasthenia gravis. The proposed listing for myasthenia gravis sub-section in the section on disorder of the peripheral nervous system will provide better guidance on the essential medicines to treat the condition.

The rationale for the request to update the observation message associated with sodium valproate (valproic acid) is based on the need to align the listing of the EML and the guidance provided through the WHO mhGAP guideline[4] which was updated in 2023. In the update, new evidence was considered regarding the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid in the womb, and a strong recommendation against its use in girls and women with childbearing potential has been issued.

Finally, two applications are being submitted for the Expert Committee's consideration for the inclusion of already listed medicines for new indications – treatment of infantile epileptic spasm (prednisolone) and trigeminal neuralgia (carbamazepine).

ANNEX: Mock-up of proposed changes to section 5.

[1] Decision WHA75(11). Follow-up to the political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases. In: Seventy-fifth World Health Assembly. Geneva: World Health Organization, 2022.
[2] Why encephalitis matters? Report of the virtual meeting, 28-29 June 2022. Geneva: World Health Organization; 2023.
[3] Assessment and management of Guillain-Barré syndrome in the context of Zika virus infection: interim guidance update. Geneva: World Health Organization; 2016.
[4] Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Geneva: World Health Organization; 2023

Approval for eDocument - HQ-2024-DOCS-eMemo-242209

Action	Action Taken By	Action Taken On (UTC)	Received On (UTC)	Comments
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Approved	MUBANGIZI, Deusdedit	06-Nov-2024 10:21 AM	07-Nov-2024 6:55 PM	To be considered by the EML Team

5. MEDICINES FOR NEUROLOGICAL DISORDERS	
5.1 Antiseizure medicines	
carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg; 400 mg.
diazepam	**Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. **Rectal solution:** 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable, dispersible):** 2m g; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. *For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
levetiracetam	**Oral solution:** 100 mg/mL **Tablet:** 250 mg; 500 mg; 750 mg; 1000 mg.
☐ lorazepam Therapeutic alternatives: - diazepam (injection) - midazolam (injection)	**Injection:** 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
magnesium sulfate*	**Injection:** 0.5 g/mL in 2 mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume). *For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
midazolam	**Solution for oromucosal administration:** 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe. **Injection*:** 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial. *For buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 30 mg/mL or 60 mg/mL **[c]**, 200 mg/mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/mL (phenytoin sodium). **Oral liquid:** 30 mg/5 mL (phenytoin). **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (phenytoin sodium). **Tablet (chewable):** 50 mg (phenytoin).

valproic acid (sodium valproate)* **Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.*	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg.
Complementary List	
ethosuximide	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*
levetiracetam	***Concentrate solution for infusion:*** *500 mg/5 mL in 5 mL vial.* ***Solution for infusion:*** *5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.*
*valproic acid (sodium valproate)** **Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.*	***Injection:*** *100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.*
5.2 Medicines for multiple sclerosis	
Complementary List	
cladribine	***Tablet:*** *10 mg.*
glatiramer acetate	***Injection (subcutaneous):*** *20 mg/mL; 40 mg/mL in pre-filled syringe.*
*rituximab** **including quality-assured biosimilars*	***Injection (intravenous):*** *500 mg/50 mL in 50 mL vial.*
5.3 Medicines for parkinsonism	
☐ biperiden Therapeutic alternatives: – trihexyphenidyl	**Injection:** 5 mg (lactate) in 1 mL ampoule. **Tablet:** 2 mg (hydrochloride).
levodopa + ☐ carbidopa Therapeutic alternatives: – benserazide (for carbidopa)	**Tablet:** 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.
5.4 Antimigraine medicines	
5.4.1 Medicines for treatment of acute migraine attacks	
acetylsalicylic acid	**Tablet:** 300 mg to 500 mg.
ibuprofen **[c]**	**Oral liquid:** 100 mg/5 mL **[c].** **Tablet:** 200 mg; 400 mg.
paracetamol (acetaminophen)	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL*; 250 mg/5 mL **[c]**. *The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. **Suppository:** 250 mg **[c].** **Tablet:** 250 mg; 325 mg; 500 mg.

	Tablet (dispersible): 100 mg, 250 mg **[c].**	
sumatriptan	**Tablet:** 50 mg	
5.4.2 Medicines for migraine prophylaxis		
☐ propranolol Therapeutic alternatives to be reviewed	**Tablet:** 20 mg; 40 mg (hydrochloride).	
5.5 Medicines for brain infections		
5.5.1 Medicines for bacterial brain infections		
amoxicillin	**Powder for injection**: 250 mg; 500 mg; 1 g (as sodium) in vial. **Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL (as trihydrate) **[c]**. **Solid oral dosage form:** 250 mg; 500 mg; 1 g (as trihydrate). **Tablet (dispersible, scored):** 250 mg; 500 mg (as trihydrate) **[c]**.	
	FIRST CHOICE	SECOND CHOICE – *Acute bacterial meningitis*
ampicillin	**Powder for injection:** 500 mg; 1 g (as sodium) in vial.	
	FIRST CHOICE	SECOND CHOICE – *Acute bacterial meningitis*
benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	
	FIRST CHOICE	SECOND CHOICE – *Acute bacterial meningitis*
chloramphenicol	**Oily suspension for injection*:** 0.5 g/mL (as sodium succinate) in 2 mL ampoule. *Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults. **Powder for injection:** 1 g (as sodium succinate) in vial.	
	FIRST CHOICE	SECOND CHOICE – *Acute bacterial meningitis*
gentamicin	**Injection:** 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.	
	FIRST CHOICE – *Acute bacterial meningitis in neonates* **[c]**	SECOND CHOICE
cefotaxime*	**Powder for injection:** 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial. *3rd generation cephalosporin of choice for use in hospitalized neonates.	
	FIRST CHOICE – *Acute bacterial meningitis*	SECOND CHOICE

<table>
<tr><td rowspan="2">ceftriaxone* a</td><td colspan="2">Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.
*Do not administer with calcium and avoid in infants with hyperbilirubinaemia.
a > 41 weeks corrected gestational age.</td></tr>
<tr><td>FIRST CHOICE
– Acute bacterial meningitis</td><td>SECOND CHOICE</td></tr>
<tr><td colspan="3">Complementary List</td></tr>
<tr><td rowspan="2">☐ meropenem* a</td><td colspan="2">Powder for injection: 500 mg (as trihydrate); 1 g (as trihydrate) in vial.
a > 3 months.</td></tr>
<tr><td>FIRST CHOICE</td><td>SECOND CHOICE
– Acute bacterial meningitis in neonates [c]</td></tr>
<tr><td colspan="3">5.5.2 Medicines for viral brain infections</td></tr>
<tr><td>☐ aciclovir
Therapeutic alternatives:
- valaciclovir (oral)</td><td colspan="2">Oral liquid: 200 mg/5 mL [c].
Powder for injection: 250 mg (as sodium salt) in vial.
Tablet: 200 mg.</td></tr>
<tr><td colspan="3">5.6 Medicines for disorders of the peripheral nervous system</td></tr>
<tr><td colspan="3">5.6.1 Medicines for Guillain-Barré syndrome</td></tr>
<tr><td>Complementary List</td><td colspan="2"></td></tr>
<tr><td>normal immunoglobulin</td><td colspan="2">Intravenous administration: 5%; 10% protein solution.</td></tr>
<tr><td colspan="3">5.6.2 Medicines for myasthenia gravis</td></tr>
<tr><td>neostigmine</td><td colspan="2">Injection: 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule.
Tablet: 15 mg (bromide).</td></tr>
<tr><td colspan="3">Complementary List</td></tr>
<tr><td>pyridostigmine</td><td colspan="2">Injection: 1 mg in 1 mL ampoule.
Tablet: 60 mg (bromide).</td></tr>
</table>