MEMORANDUM

From:	Director, MSD	**To:**	Director, HPS	**Date:**	28 May 2021
Our ref:	WHOHQ-E19-81-17	**Attention:**			
Your ref:		**Through:**			
Originator:	Dr Tarun Dua, Unit Head, BRH	**Subject:**	Meeting of the 23rd Expert Committee on Selection and Use of Essential Medicines.		

Please find enclosed the comments from the Department of Mental Health and Substance Use on the applications as listed below for updating the 2019 Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc).

- Methylphenidate – addition to the EML and EMLc for attention deficit hyperactivity disorder;
- Paliperidone and risperidone (long-acting injection) – addition to the EML for schizophrenia and related psychotic disorders;
- Sumatriptan – addition to the EML for treatment of migraine;
- Sodium valproate – changes to current listings to include cautionary note about use during pregnancy and in women of child-bearing potential;
- Correspondence from the Multiple Sclerosis lnternational Federation on disease modifying therapies for multiple sclerosis.

Please contact Tarun Dua (duat@who.int) in case of any queries.

Ms Dévora Kestel

ENCL: 1

cc: Dr Benedikt Huttner, Team Lead, MIA/EML

Dr Mark Van Ommeren, Unit Head, MSD/MHE

World Health Organization

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Action	Action Taken By	Received On(UTC)	Action Taken On(UTC)	Comments	Attachments
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COMMMENTS FROM THE DEPARTMENT OF MENTAL HEALTH AND SUBSTANCE USE

1. Methylphenidate – addition to the EML and EMLc for attention deficit hyperactivity disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder affecting 7% of children and adolescents globally. It can have important impacts on several aspects of children's current and future lives, including their educational achievements, wellbeing and quality of live. Management plans for ADHD in children involves psychosocial interventions such as behavioural interventions and parent training along with environmental accommodations and may include pharmacological treatment.

A proposal for inclusion of methylphenidate on the WHO Model List of Essential Medicines for Children was considered by WHO Expert Committee on the Selection and Use of Essential Medicines for the 2019 Essential Medicines Lists update. In 2019 the Expert Committee did not recommend inclusion of methylphenidate on the Model Lists for the treatment of ADHD due to uncertainties in the estimates of benefit, and concerns regarding the quality and limitations of the available evidence for both benefit and harm.

The proposal for inclusion of Methylphenidate Hydrochloride in the WHO Model List of Essential Medications for Children raises an important concern about inadequate access to treatment for children with ADHD, which should be carefully considered along with considerations on appropriate and safe use of medications.

The application provides an overview of the evidence on benefits and harms, including potential misuse. The application points to the findings of a review conducted by Cortese et al. in 2018 which included network meta-analysis of RCTs on pharmacological treatment of ADHD across the lifespan. The quality of the evidence of the RCTs on methylphenidate on the primary outcome (clinicians rating) was judged as moderate by Cortese et al. The authors concluded that, considering all the included outcomes related to efficacy/safety, methylphenidate should be considered the first line pharmacological option for ADHD in children and adolescents. However, only short-term (12 weeks timepoints) outcomes for efficacy and tolerability were analyzed and presented. It is also important to note that the review by Cortese et al. included studies with children 5 years or older and that sensitivity analysis by age (children vs adolescents) was not possible. The application doesn't include any comparison of pharmacological with psychosocial interventions. A Cochrane review (Storebø et al, 2018) on assessment of adverse events in nonrandomized studies reported that methylphenidate may be associated with a number of serious adverse events as well as a large number of nonserious adverse events in children and adolescents, though the certainty of evidence is very low. Nonmedical use of methylphenidate is also a public health concern (Faraone SV et al, 2020).

NICE guidelines recommend to offer medication (methylphenidate as the first line medication) for children aged 5 years and over and young people only if their ADHD symptoms are still causing a persistent significant impairment in at least one domain after environmental modifications have been implemented and reviewed and that they and their parents and carers have discussed information

about ADHD. Methylphenidate treatment should be initiated by a healthcare professional with training and expertise in diagnosing and managing ADHD.

The mhGAP guidelines include the use of methylphenidate in the management protocol of children at least 6 years old with a diagnosis of ADHD. It is provided as second-line treatment (after parent training and behavioural interventions) and to be initiated by a specialist. The mhGAP guideline update process is underway and this recommendation will be examined to consider if they need to be modified. Important considerations will relate to health systems capacity to enforce and implement protocols for ADHD diagnosis, to prescribe and initiate methylphenidate treatment, to ensure careful clinical monitoring for side effects, clinical response, adherence, treatment acceptability, and dose adjustment. Risks for methylphenidate misuse and risks for overmedicalization and overtreatment of behavioural problems in children will also be considered.

2. Paliperidone and risperidone (long-acting injection) – addition to the EML for schizophrenia and related psychotic disorders

MSD has been approached on various occasions by various actors (eg MSF, UNHCR, CBM) about the uncertainty of future availability of fluphenazine, currently the only long-acting injectable antipsychotic on the EML. Long-acting injectable antipsychotics (LAIs) are an established treatment option for schizophrenia, and are recommended in existing WHO (mhGAP) guidelines. The systematic review included in the application by the WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation has since then been published in the peer reviewed literature (Ostuzzi et al, 2021, American Journal of Psychiatry). Further, a very recently published new systematic review by a different research group showed significant benefits of LAIs versus oral antipsychotics in preventing hospitalisation or relapse (Kishimoto et al 2021, Lancet Psychiatry), providing further evidence of the important to have LAI antipsychotics available in health services around the world.

3. Sumatriptan – addition to the EML for treatment of migraine

Migraine is a common disabling primary headache disorder characterized by recurrent moderate to severe pain generally occurring on one side of the head. It is a cause of pain and disability and has a substantial societal burden. Many epidemiological studies have documented its high prevalence and socio-economic and personal impact (GBD 2019).

The application provides detailed evidence of the efficacy and safety of Sumatriptan in the adult population. Many evidence-based guidelines, issued by the international scientific societies and agencies, recommend sumatriptan or other triptans as first-line drug in adults with acute migraine. While trials comparing sumatriptan with placebo demonstrate significant effect on most clinically meaningful outcomes, the evidence comparing sumatriptan with other NSAIDs show inconsistent results. Sumatriptan may be a particularly advantageous therapeutic option in pregnant women when most common analgesics are contraindicated or not effective. Sumatriptan can be safely administered to breastfeeding women. Sumatriptan could be a useful therapeutic option, whenever medications already listed in the EML are contraindicated, not tolerated or ineffective.

4. Sodium valproate – changes to current listings to include cautionary note about use during pregnancy and in women of child-bearing potential

Sodium valproate is used to treat epilepsy and bipolar disorder, conditions for which they are included on the WHO Model List of Essential Medicines, and have regulatory approval. Sodium valproate is recommended in the mhGAP guidelines for mental, neurological, and substance use (MNS) disorders for the management of epilepsy and bipolar disorder. In the mhGAP guidelines update 2015, there is a strong recommendation to avoid its use in women who are pregnant or breastfeeding.

The recommendations state:

- *For manic episode in bipolar disorder:* Avoid valproate, (lithium and carbamazepine) during pregnancy and breast feeding due to risk of birth defects
- *For epilepsy*: Women with epilepsy should have seizures controlled as well as possible with the minimum dose of antiepileptic drug taken in monotherapy, wherever possible. Antiepileptic drug polytherapy should be avoided. Valproic acid should be avoided if possible.

The mhGAP guideline update process is underway and these recommendations will be examined to consider if they need to be modified and/or reinforced to reflect latest evidence.

The application provides evidence of the harmful effects of valproate use in this population based on the Summary of Product Characteristics (SmPC). Two Cochrane reviews are important to add to this evidence base:

Weston_J, Bromley_R, Jackson_CF, Adab_N, Clayton-Smith_J, Greenhalgh_J, Hounsome_J, McKay_AJ, Tudur Smith_C, Marson_AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224.

Bromley_R, Weston_J, Adab_N, Greenhalgh_J, Sanniti_A, McKay_AJ, Tudur Smith_C, Marson_AG. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236.

The application also notes that based on the available data, it is not possible to establish a threshold dose for valproate below which no risk of developmental disorders exists and this continues to require further research.

While most of the evidence and regulatory measures described in the application are from UK and EU Member States, the risks with valproate when prescribed to women and girls of child bearing potential are equally relevant, to all women, worldwide.

On the proposal to add cautionary Note attached to Valproate's listing in the EML and EMLc, the evidence provided in the application supports this proposal. On the proposal to transfer of Valproate to complementary listing, the application does not discuss the benefits of valproate which are well established. Moving valproate to the complementary list would make it less accessible to populations

that can potentially benefit from its use i.e. children or men where valproate may be the choice of medication. Furthermore, specialist prescribing by a neurologist is not possible in many settings where resources are limited.

5. **Correspondence from the Multiple Sclerosis International Federation (MSIF) on disease modifying therapies for multiple sclerosis**

In 2019, the WHO Expert Committee provided feedback on the application by MSIF to add disease modifying therapies (DMTs) for multiple sclerosis to the WHO EML. Feedback included the need to review commonly used DMTs, clearly defining the superiority of the proposed medications and the inclusion of international MS guidelines.

MSIF is actively working on addressing these comments and is also planning to review the existing evidence available for the off-label drugs azathioprine and rituximab which are used in clinical practice - particularly in low resource settings. WHO secretariat will be available to provide technical support and advice to MSIF as they work on the revised application.

The past 15 years have seen an unprecedented development of new treatments for MS with varying benefits, harms and affordability. It should be emphasized that MS is a complicated disease with different presentations and phases that can frequently evolve such as relapsing remitting, secondary progressive, primary progressive and clinically isolated syndrome. Thus, the application process would need to evaluate the therapies to treat the different stages and activity of the disease including paediatrics and pregnant individuals, and those with comorbidities. Systematic reviews including network meta-analysis should be considered as well as GRADE methodology for development of the revised application.