Comments from the Department of Mental Health, Brain Health and Substance Use

Proposal for inclusion of Methylphenidate to the WHO Model List of Essential Medications (EML) & the Model List of Essential Medications for Children (EMLc) for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents between the ages of 6 and 17 years

The proposal to add Methylphenidate to the list of the EMLc and EML for the treatment of children and adolescents between the ages of 6 to 17 years with attention deficit/hyperactivity disorder (ADHD) raises an important concern about inadequate access to care for children and adolescents with ADHD, which should be carefully considered along with considerations on appropriate and safe use of medications.

Two previous applications for inclusion of methylphenidate in the EML and EMLc for the treatment of ADHD were considered by Expert Committees on the Selection and Use of Essential Medicines for the 2019 Essential Medicines Lists update and the 2021 Essential Medicines Lists update. In 2019 and in 2021 the Expert Committees did not recommend inclusion of methylphenidate in the Model Lists for the treatment of attention-deficit hyperactivity disorder (ADHD) due to concerns about the quality of the evidence presented on benefits and harms.

Specifically, the Expert Committee requested by WHO to provide feedback on this application in 2021 recommended that, for any future consideration for the listing of methylphenidate, the following would be informative: evidence for the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings.

The current application discusses the points above providing an overview of the available evidence on short- and long-term benefits and harms, including risks for non-medical use and diversion for non-medical purposes due to psychoactive and dependence-producing properties along with considerations on health systems capacity for appropriate prescribing and monitoring of treatment.

Evidence from RCTs on long-term benefits of methylphenidate remain limited, with only two clinical RCTs *(1;2)* providing data on benefits for methylphenidate treatment of 12 months or longer in children and adolescents and a randomized discontinuation trial *(3)*. Both clinical RCTs have limitations, including absence of blinding and absence of placebo control groups. Both RCTs point towards reduced severity of ADHD symptoms although the Multimodal Treatment Trial did not indicate that methylphenidate treatment (alone or in combination) at timepoints after 14 months was superior to the other groups. Findings from observational studies on functional outcomes are also discussed.

There is limited evidence on adverse events for long-term treatment, with two RCTs and observational studies finding no association between methylphenidate treatment and serious adverse events. There is mixed evidence concerning the impact of cumulative, long-term treatment with methylphenidate and alterations in somatic growth and specific cardiovascular events. There is evidence (certainty of evidence: very low quality) of increased non-serious adverse events and methylphenidate treatment (short-term) including headache, decreased appetite, weight and body mass index, increase in diastolic pulse and diastolic blood pressure and sleep problems.
The application discusses data on non-medical use of stimulants. A systematic review *(4)* on the non-medical use and diversion for non-medical purposes of prescription stimulants reported that rates of

these behaviors varied widely across studies, with prevalence rates of nonmedical use ranging from 2.1% to 58.7%.

In addressing the request to discuss system capacity for prescribing and monitoring treatment, the application provides data from WHO Mental Health Atlas 2020 pointing to increased capacity to offer specialist supervision at primary health care in countries.

The application refers also to the updated WHO mhGAP guidelines recommendation (2023) on pharmacological treatment for ADHD, which reinforced the importance to consider the health system's capacity to implement protocols for ADHD diagnosis and treatment.

In the context of the update process for mhGAP guidelines in 2022-2023, the recommendation pertaining to methylphenidate treatment in older children and adolescents with ADHD was modified to make explicit the aspects that needs to be assessed for methylphenidate to be considered as part of individual management plans. Specifically, "For children 6 years old and above and adolescents who have an attention deficit hyperactivity disorder (ADHD) diagnosis, methylphenidate may be considered provided that:

- ADHD symptoms are still causing persistent significant impairment in at least one domain of functioning (education, interpersonal relationships, occupation), after the implementation of environmental modifications in schools, at home or in other relevant settings;
- A careful assessment of the child/adolescent has been conducted;
- The child/adolescent and the caregivers, as appropriate, have been informed about ADHD treatment options and supported in supported decision-making;

Methylphenidate prescription is made by, or in consultation with, a specialist."

The above mhGAP updated recommendation is rated as "conditional" in terms of "strength of recommendation" and is informed by "low certainty of evidence".
The mhGAP recommendation provides additional considerations to help ensure that methylphenidate treatment is considered in the context of comprehensive individualized care plans and when there is capacity to undertake careful assessment and monitoring, including of any adverse effects.

mhGAP considerations includes the following "Methylphenidate prescription is made by, or in consultation with, a specialist. Children and adolescents receiving methylphenidate should be maintained under close clinical monitoring for improvement in symptoms and prevention of adverse events. A specialist care provider trained on management of ADHD should reassess the child's/adolescent's management plan for ADHD at least once per year. Additionally, whenever possible methylphenidate treatment should be combined with brief parent behavioral therapies and psychosocial interventions that may attenuate the impairment stemming from symptoms, such as organizational skills training and social skills and cognitive training."

References:

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2. Barragan E, Breuer D, Dopfner M. Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten Disord. 2017;21(5):433-41 (https://doi.org/10.1177/1087054713518239).

3. Matthijssen AM, Dietrich A, Bierens M, Kleine Deters R, van de Loo-Neus GHH, van den Hoofdakker BJ et al. Continued Benefits of Methylphenidate in ADHD After 2 Years in Clinical Practice: A Randomized

Placebo-Controlled Discontinuation Study. Am J Psychiatry. 2019;176(9):754-62 (https://doi.org/10.1176/appi.ajp.2019.18111296).Faraone SV,

4. Rostain AL, Montano CB, Mason O, Antshel KM, Newcorn JH. Systematic Review: Nonmedical Use of Prescription Stimulants: Risk Factors, Outcomes, and Risk Reduction Strategies. J Am Acad Child Adolesc Psychiatry. 2020;59(1):100-12 (https://doi.org/10.1016/j.jaac.2019.06.012).