A.19 Methylphenidate – EML and EMLc

Reviewer summary	☐ Supportive of the proposal ☒ Not supportive of the proposal Justification (based on considerations of the dimensions described below): This application proposes the addition of **methylphenidate** as an individual medicine 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). Two previous applications made by other independent groups were rejected mainly for the lack of evidence about efficacy and safety in the long-term given that ADHD can be a chronic condition. ADHD is a neurodevelopmental disorder characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that is outside the limits of normal variation expected for age and level of intellectual development and has direct negative impact on academic, occupational, or social functioning. Based on low certainty evidence, the 2023 mhGAP guideline for treatment of ADHD **conditionally** recommends methylphenidate as a treatment option in the context of a management plan that addresses psychosocial risks and vulnerabilities and environmental factors that have an impact on symptoms and functioning. Specifically, 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 decision-making; - methylphenidate prescription is made by, or in consultation with, a specialist. See page 28 of the guidelines for evidence summary. Ref: https://iris.who.int/bitstream/handle/10665/374250/9789240084278-eng.pdf?sequence=1 In the short-term, compared to placebo or no-intervention methylphenidate may improve teacher-rated ADHD symptoms and general behaviour in children and adolescents with ADHD, with no substantial increased risk of serious adverse events. Non-serious unwanted adverse events include sleeping problems and decreased appetite. Certainty of the evidence for all outcomes was judged very low by the review authors and moderate by the Application authors. No clear effect on quality of life has been detected. Few RCTs examined long-term treatment (more than 6 months) - all had some methodologic limitations – suggested a reduced severity of ADHD symptoms over long periods of time as rated by parents, teachers, and/or independent investigators. Pharmacoepidemiologic data provide evidence of beneficial 'real-world' functional outcomes associated with long-term use of methylphenidate. However, also these studies suffer of intrinsic methodological limitations. Costs of medication appears not to pose concerns as prices are generally low and generic formulation of short-acting methylphenidate are available. It should be however highlighted the need for proper resources to enforce and implement protocols for ADHD diagnosis, prescribe and initiate methylphenidate by or in close consultation with a specialist, and to ensure careful clinical monitoring for side-effects, clinical response, adherence, treatment acceptability, and dose adjustment. Indeed, among the concerns leading to the rejection of previous applications, there were the feasibility of health care systems to provide the diagnostic and monitoring processes required for methylphenidate prescription. This Reviewer recognises that methylphenidate has a favourable and meaningful balance of benefits to harms at least in the short-term and is considered a standard approach for some subset of children and adolescents with ADHD in many countries. Undoubtedly, concerns remain on the long-term effects, as in general for pharmacological treatment of mental disorders for younger children. Moreover, even if the inclusion of methylphenidate on the WHO Model List may contribute to increase access to this medication in many countries, the adequate prescription and monitoring can

	only occur in those settings where reference centres for ADHD management are active. This approach is also important to reduce the risks associated with its non-medical use and diversion. These concerns warrant a thorough discussion by the Expert Committee, before the decision to support the inclusion of methylphenidate on the WHO Model List.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? Two medicines currently included on the Model Lists that may be used off-label for ADHD in children and adolescents (bupropion listed for nicotine dependence and clomipramine for obsessive-compulsive disorder). (https://list.essentialmeds.org/) The current Application does not support the inclusion of these medicines for ADHD	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? An updated Cochrane review summarised 212 trials (16,302 participants randomised) comparing methylphenidate versus placebo or no intervention in children and adolescents aged 18 years and younger with a diagnosis of ADHD. - teacher-rated ADHD symptoms: standardised mean difference (SMD) −0.74, 95% confidence interval (CI) −0.88 to −0.61; IR = 38%; 21 trials; 1728 participants; very low-certainty evidence), corresponding to a mean difference (MD) of −10.58 (95% CI −12.58 to −8.72) on the ADHD Rating Scale (ADHD-RS; range 0 to 72 points). This difference exceeds the minimal clinically relevant difference considered to be a change of 6.6 points on the - serious adverse events: risk ratio (RR) 0.80, 95% CI 0.39 to 1.67; IR = 0%; 26 trials, 3673 participants; very low-certainty evidence). Ref: https://doi.org/10.1002/14651858.CD009885.pub3 At 14 months, the combination of methylphenidate and behavioral treatment (parent, school, and child components, with therapist involvement gradually reduced over time) showed a greater decrease in teacher-ratings (standardized mean difference [SMD] -0.45; 95% CI -0.7 to -0.2) and parent-ratings of inattention (SMD -0.57; 95% CI -0.81 to -0.32), hyperactivity-impulsivity (SMD -0.58; 95% CI -0.82 to -0.33), and aggression (SMD -0.42; 95% CI -0.66 to -0.17) compared to those in behavioral treatment alone. Ref: https://doi.org/10.1001/archpsyc.56.12.1073 The Application also mentioned evidence from several observational studies. Two pharmacoepidemiologic studies demonstrated reduced mortality, in particular due to reduced non-accidental injuries, amongst those receiving medicines for ADHD (including methylphenidate) in Sweden and Canada. A systematic review summarising 40 studies, mostly register-based case-cohorts, indicated that methylphenidate was associated with decreased odds of worse academic outcomes (odds ratio [OR] 0.8; 95% CI 0.76, 0.84) and accidental injuries (OR 0.72; 95% CI 0.59, 0.87).	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? Insomnia and nervousness are the most reported adverse effects in patients using methylphenidate. Long-term treatment with methylphenidate has been associated with slight growth deficit, particularly for height, although causal effects is controversial. Methylphenidate can increase both heart rate and diastolic blood pressure acutely and there are concerns for its use in children and adolescents over the long-term. Monitoring growth and cardiac function is recommended to detect any medication induced changes and weighed them against treatment benefits. There is some evidence of an increased risk of suicide attempts in the period immediately before the start of methylphenidate treatment, however causality has not been confirmed. Nonmedical use and diversion of methylphenidate as other psychostimulants may be problematic in some countries.	☒ Yes ☐ No ☐ Not applicable

25th WHO Expert Committee on Selection and Use of Essential Medicines
Expert review

Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? To ensure appropriate use of the medicine, all the following requirements should be met: - Children and adolescents must be at least 6 years old and younger than 18 years old. - Children and adolescents must have a diagnosis of ADHD according to criteria outlined in ICD-11 or the DSM-5. - The diagnosis of ADHD should be made by a licensed professional with training and expertise in diagnosing ADHD. Attention to psychosocial factors and a psychosocial perspective is essential - Practitioners should ensure that the symptoms do not respond to measures such as adapting features in the child's environment (not a diagnostic requirement in ICD-11 but recommended in the mhGAP guidelines)	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? The studies presented by the Application suggest that methylphenidate is a cost-effective treatment option over placebo or no treatment across different settings and countries.	☐ Yes ☒ No ☐ Not applicable
Is the medicine available and accessible across countries? At least 53 countries (including low- and middle-income countries) currently include methylphenidate in their national essential model lists Ref: https://global.essentialmeds.org/dashboard/medicines/1196	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval? In several countries, prescribing and dispensation is subject to restrictions that aim to minimize both diversion and nonmedical use	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable