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): **Supportive** of the application to include **methylphenidate on the WHO Model List of Essential Medicines (EML)** for children and adolescents with ADHD — provided that implementation includes safeguards for diagnosis, training, and monitoring. ADHD is a prevalent and disabling condition globally, affecting over 47 million young people, including nearly 5 million in Sub-Saharan Africa. Methylphenidate has demonstrated moderate-to-large benefits in reducing core ADHD symptoms, with supporting evidence from randomized trials and real-world observational studies. While there are manageable risks such as appetite loss and sleep disturbances, serious adverse effects are rare and can be mitigated with proper monitoring. Including methylphenidate on the list would promote equitable access, especially in low- and middle-income countries where treatment gaps persist. It aligns with WHO's mhGAP recommendations and supports the scaling of mental health care into primary settings. With safeguards for diagnosis, monitoring, and misuse prevention, this inclusion would improve health, education, and social outcomes for millions of children worldwide.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) An application was previously submitted but was not favourable. The expert committee made a request for evidence acquired over long periods of time, ideally more than 52 weeks given that ADHD can be a chronic condition, requiring long-term management. The current application has considered this.	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) Yes, with qualifications. There is moderate to strong evidence for short-term efficacy and some supportive evidence for long-term effectiveness, though the number of long-term RCTs remains limited.	☒ Yes ☐ No ☐ Not applicable

Criterion	Assessment
Multiple high-quality studies	Numerous short-term RCTs reviewed by Cochrane (2023), showing consistent moderate-to-large effects.
Long-term follow-up data	Limited: Only **two RCTs** with ≥12-month follow-up (MTA study and a Mexican trial). Additional **observational studies** (e.g., ADDUCE, Swedish registry) support long-term use.
GRADE rating concerns	Authors argue Cochrane's "very low" rating is overly stringent. Justification provided for **moderate certainty** rating based on teacher and parent reports.
Real-world effectiveness	Pharmacoepidemiological studies show reduced mortality, injuries, and improved academic outcomes.

SUMMARY OF FINDINGS

Summary of findings 1. Methylphenidate compared with placebo or no intervention for children and adolescents with ADHD

Methylphenidate compared with placebo or no intervention for ADHD

Patient or population: children and adolescents (up to and including 18 years of age) with ADHD
Settings: outpatient clinic, inpatient hospital ward and summer school
Intervention: methylphenidate
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no intervention	Methylphenidate				
ADHD symptoms: all parallel-group trials and first-period cross-over trials ADHD Rating Scale (teacher-rated) Average trial duration: 68.7 days		Mean ADHD symptom score in the intervention groups corresponds to a mean difference of −10.58 (95% CI −12.58 to −8.72) on ADHD Rating Scale	**SMD** **−0.74** (−0.88 to −0.61)	1728 (21 trials)	⊕⊙⊙⊙ **Very low**[a,b]	The analysis was conducted on a standardised scale with data from studies that used different teacher-rated scales of symptoms (Conners' Teacher Rating Scale (CTRS), Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale, The Swanson, Nolan and Pelham (SNAP) Scale - Teacher, Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)). We translated the effect size on to the ADHD Rating Scale from the SMD.
Proportion of participants with one or more serious adverse events	**Trial population**		**RR 0.80** (0.39 to 1.67)	3673 (26 trials)	⊕⊙⊙⊙ **Verylow**[a,c]	TSA RIS = 9349 TSA showed a RR of 0.91 (TSA-adjusted CI 0.31 to 2.68)
	8 per 1000	**6 per 1000** (5 less to 5 more)				

Adequate evidence exists**, especially for short-term effectiveness, and there is** supportive albeit limited long-term evidence**. The application meets the WHO's general threshold, though a call for further long-term RCTs remains valid.**

Does adequate evidence exist for the safety/harms associated with the proposed medicine?

(e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)

☒ Yes ☐ No ☐ Not applicable

Yes, with caveats.
The application presents substantial evidence **on safety and harms from** multiple high-quality studies**, including both** randomized controlled trials (RCTs) **and** long-term observational studies**. However, some areas (e.g., cardiovascular risk) warrant** continued monitoring**.**

Aspect	**Summary of Evidence**
Short-term non-serious AEs	Well-documented in the 2023 Cochrane review (35 RCTs). Noted AEs: decreased appetite, sleep issues, mild BP/HR increases. Rated as "very low certainty" by Cochrane, but this was challenged by applicants.
Serious AEs	Long-term RCTs (MTA) and observational data (ADDUCE) show **no significant increase** in serious AEs (e.g., suicidality, psychosis, sudden death).
Growth concerns	Mixed evidence. Some studies (e.g., 2021 meta-analysis) show slight reductions in height/weight gain. Others (e.g., ADDUCE) find no significant growth suppression.
Cardiovascular effects	Observational studies (e.g., Sweden registry, ADDUCE) suggest **small increases in BP, HR, and potential cumulative risk** with long-term, high-dose use.
Neuropsychiatric events	No strong association with suicidal ideation or psychosis. Mood improved over time in many children on methylphenidate (ADDUCE data).

Yes, adequate evidence exists **for the safety/harms of methylphenidate. While short-term adverse effects are well-characterized and generally non-serious, long-term safety (especially cardiovascular and growth effects) is supported by** observational evidence**, with a** need for continued monitoring and patient assessment**.**

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Expert review

Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?

☒ **Yes** ☐ **No** ☐ **Not applicable**

Yes, the balance is favourable**, especially when treatment is provided under appropriate diagnostic, monitoring, and follow-up conditions.**

Category	**Key Findings**
Benefits	Strong short-term symptom improvement (SMD -0.7), improved academic productivity, and some gains in cognitive function. Observational data suggest reduced risks of injuries and mortality.
Harms	Non-serious adverse effects are relatively common but manageable (e.g., appetite loss, sleep disturbance). Long-term concerns about growth and cardiovascular risks exist but are **low in magnitude** and **monitorable**.
Quality of Evidence	Short-term efficacy: **moderate certainty** (revised from Cochrane's very low). Long-term effectiveness and safety: Supported by RCTs and large-scale observational studies.
Context of Use	WHO mhGAP guidelines support use in a structured management plan. Implementation feasibility improving via task-shifting and primary care integration in LMICs.

Methylphenidate presents a favourable benefit-to-harm ratio **for children and adolescents with ADHD, when used within a framework of accurate diagnosis, appropriate prescribing, and regular monitoring. The evidence supports its inclusion on the WHO Model List of Essential Medicines.**

Are there any special requirements for the safe, effective and appropriate use of the medicines?

☒ Yes ☐ No ☐ Not applicable

(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)

Yes. **The proposal clearly outlines multiple requirements necessary for appropriate use, especially in low- and middle-income country (LMIC) contexts.**

Requirement Type	**Details**

Diagnostic Requirements	Diagnosis must be made by a licensed professional using **ICD-11** or **DSM-5** criteria. Requires full psychosocial and developmental assessment across settings (home, school, etc).
Monitoring Tests	Baseline and periodic **cardiovascular assessments** (e.g., blood pressure, heart rate). ECG and cardiology consults recommended if risk factors (e.g., family history of sudden death).
Specialized Provider Training	Providers must be trained to assess ADHD, rule out differential diagnoses, and evaluate psychosocial context. Training for **dose titration, side effect monitoring, and follow-up** needed.
Health System Infrastructure	Must include **systems for regular follow-up**, dose adjustment, and management of side effects. Emphasis on **task-sharing** and **supervision** within primary care per **mhGAP**.
Regulatory Controls	Being a controlled substance, methylphenidate requires **strict prescription protocols** to prevent misuse/diversion.

The safe and effective use of methylphenidate requires trained providers**,** structured diagnostic and follow-up procedures**, and** health system capacity **(particularly for monitoring and regulation). These are feasible with scaling efforts such as those promoted by** WHO mhGAP**.**

Are there any issues regarding price, cost-effectiveness and budget implications in different settings?

☒ Yes ☐ No ☐ Not applicable

Brazil (2014 Data):

- **Immediate-release methylphenidate (MPH-IR) 10 mg (20 pills) is acquired by the public health system at a maximum price of I$8.43, equating to I$0.42 per pill.**

United States:

- **Generic methylphenidate is available for as low as $9.61, which is 83% off the average retail price of $54.92 for the most common version, by using a GoodRx coupon.**

Low- and Middle-Income Countries (LMICs):

- **In LMICs, the cost and supply of ADHD medications, including methylphenidate, act as barriers. Medication use often relies on non-government sources, and there is a lack of resources for child and adolescent psychiatry, along with poor recognition to diagnose ADHD among doctors.**

Cost-Effectiveness Analyses

• **Brazil:**
  ○ **A Markov model comparing MPH-IR to no treatment over a 6-year horizon found incremental cost-effectiveness ratios (ICERs) of I$9,103 per quality-adjusted life year (QALY) for children and I$11,883/QALY for adolescents.**
• **Netherlands:**
  ○ **Switching sub-optimally treated patients from immediate-release methylphenidate (IR-MPH) to extended-release methylphenidate (ER-MPH) regimens led to per-patient cost savings of €4,200 to €5,400 over a 10-year treatment span.**
• **Australia:**
  ○ **Simulation modeling indicated that methylphenidate has an ICER of A$15,000 per disability-adjusted life year (DALY) saved, suggesting cost-effectiveness for childhood ADHD treatment.**
 	
Budget and Implementation Considerations
• **Affordability in LMICs:**
  ○ **Despite evidence of cost-effectiveness, affordability remains a significant challenge in LMICs due to low mental health budgets and high out-of-pocket expenditures.**
• **Supply Chain and Pricing Policies:**
  ○ **The WHO/Health Action International project highlights that medicine prices in LMICs can be disproportionately high, with essential medicines being up to 80 times more expensive than in high-income countries. Factors include retail markups and inefficient procurement practices.**
 	
While methylphenidate is generally cost-effective for treating ADHD in children and adolescents across various settings, its affordability and accessibility in LMICs are hindered by high medication costs, limited public funding, and supply chain challenges. Addressing these issues through policy interventions, such as inclusion in national essential medicines lists and implementation of pricing regulations, is crucial for improving access.	

Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) Methylphenidate, a central nervous system stimulant commonly prescribed for Attention Deficit Hyperactivity Disorder (ADHD), has been widely used since the 1990s and is available in various formulations across numerous countries. However, its availability and accessibility vary significantly due to regulatory classifications, supply chain challenges, and differing national policies. **Global Availability and Accessibility**	☐ Yes ☒ No ☐ Not applicable

Regulatory Status: Methylphenidate is classified as a controlled substance in many countries, leading to stringent regulations on its prescription and distribution. For instance, in the United States, it is a Schedule II controlled substance, while in the United Kingdom, it is classified as a Class B drug. These classifications often necessitate special prescribing practices and monitoring, which can affect accessibility**.** Wikipedia **Supply Chain Challenges:** Recent years have seen global shortages of methylphenidate, attributed to factors such as increased demand, manufacturing delays, and regulatory constraints. In Australia, shortages of various methylphenidate products, including Concerta and Ritalin LA, have been reported, with some expected to persist until late 2025. Similarly, New Zealand has experienced a 140% increase in demand over two years, leading to anticipated supply gaps throughout 2025. In the United States and the United Kingdom, patients have faced difficulties obtaining their medications due to these shortages. **Generic Availability:** While generic versions of methylphenidate are available and can improve accessibility, shortages have affected both brand-name and generic formulations. In the U.S., for example, generic versions of ADHD medications, including methylphenidate, have remained in shortage, impacting patients' ability to access treatment. **Access Programs and Initiatives:** Efforts to improve access include the inclusion of methylphenidate in the WHO's Mental Health Gap Action Programme (mhGAP), which aims to scale up services for mental, neurological, and substance use disorders, particularly in low- and middle-income countries. However, the absence of methylphenidate from the WHO Model List of Essential Medicines has been cited as a barrier to its accessibility in many regions. The Lancet **Conclusion** While methylphenidate is available in many countries, its accessibility is hindered by regulatory restrictions, supply chain issues, and inconsistent inclusion in national essential medicines lists. Addressing these challenges requires coordinated efforts, including regulatory harmonization, improved supply chain management, and inclusion in essential medicines lists to ensure equitable access to this critical medication for individuals with ADHD.	
Does the medicine have wide regulatory approval? Yes, methylphenidate has wide regulatory approval **across many countries, including high-, middle-, and some low-income settings, though its regulatory status as a** controlled substance **affects its prescription and distribution.** Methylphenidate is widely approved **by national and international regulatory bodies for the treatment of ADHD, including in children and adolescents. However, because it is classified as a controlled substance in most jurisdictions, its use is accompanied by** strict prescribing regulations**, which may limit accessibility in certain regions. In Sub-Saharan African countries,** some countries allow importation but **lack regulatory clarity**, capacity for monitoring, or inclusion in national formularies.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable