A.21	Methylphenidate for Attention-Deficit/Hyperactivity Disorder
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: The worldwide prevalence of ADHD has been estimated as 2% to 7%, with the average of 5% (Polanczyk et al., 2007; Sayal, Prasad, Daley, Ford, & Coghill, 2018). This indicates that the prevalence has remained consistent over the years and does not indicate a public health need.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Stimulants (which contain various forms of methylphenidate and amphetamine), are the best-known and most widely used ADHD medications. Nonstimulants were approved for the treatment of ADHD in 2003 in the US (Strattera (atomoxetine), Intuniv (guanfacine), and Kapvay (clonidine)).
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). The applicants report data from meta-analyses conducted on adolescents and children (up to January 2018), though the upper limit for the adolescent age group differs from study to study. In summary, methylphenidate showed higher SMDs compared with placebo and was slightly inferior to amphetamines in terms of efficacy on ADHD core symptoms rated by clinicians. The quality of the evidence from RCTs of methylphenidate, rated with the GRADE system, was deemed of moderate level for the comparison methylphenidate vs placebo, clinicians' ratings. showing a benefit of methylphenidate over placebo. Overall, the quality of the data is of too low quality to determine the extent of benefit of methylphenidate. Furthermore, long-term efficacy studies of high quality are missing. The quality of the evidence for adults is very low and cannot therefore be considered reliable to take informed decisions Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Limited studies in low resourced settings. Some diversity in settings and populations presented.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Applicants have undertaken a systematic review in November 2020 and have selected 25 studies and review articles to extract the evidence, and 5 were excluded thereafter. The application did not provide a list of these selected publications within the text.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: There are a number of risks associated with the use of methylphenidate, including cardiovascular risks, a worsening of psychiatric symptoms, and suppression of growth. The quality of the overall evidence does not allow to determine the overall absolute risk of the medicine. The absence of sufficient data on long-term treatment is also an obstacle to determining risks. The applicants mention these other risks: • Dependence and/or abuse may develop. • Tolerance to therapeutic effects may develop in some patients • Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Uncertain as low quality of evidence does not provide substantive benefit outcomes. As such, current evidence points to risks outweighing benefits.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Low quality of evidence
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Diagnosis needs specialist on child/adolescent/ adult Psychiatrist. Extremely well-trained professionals in the diagnosis, management and treatment of ADHD are required to avoid under/over-treatment. Monitoring of risks (e.g. cardiovascular, growth, BP, anorexia) is also required. Prevention of substrate abuse by the individual/family members/others require careful diagnosis and follow up.

Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: However, many regulatory agencies have issued warnings or advice on monitoring patients during treatment, for example, for cardiovascular, hepatic, and psychiatric risks. Some agencies have implemented patient registries for the use of the drug. Public health officials have noted that there is an important risk of abuse and misuse of methylphenidate in communities.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: World Health Organization's, mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (World Health Organization, 2018b): "Consider methylphenidate for hyperkinetic disorder only if psychosocial interventions have failed, the child has been carefully assessed and is at least 6 years old, and conditions whose management can be complicated by methylphenidate have been ruled out. Use of stimulant medication must always be part of a comprehensive treatment plan that includes psychological, behavioural and educational interventions"
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Methylphenidate is affordable and generics are available.
Any additional comments	None
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	The reviewer recommends that methylphenidate is not included in the core list of EML or EMLc but rather the complementary list due to (i) the difficulty in determining risk/benefit based on submitted evidence, (ii) the strong possibility of under-and over-diagnosis of the disorder, (iii) current WHO guidelines indicate that the product should be used when other remedial non-pharmacological measures are taken (psychological, educational, social) and even then, in combination with these interventions. This is a controlled substance requiring correct legal mechanism in place to prevent diversion.
References (if required)	None. Covered in application