A.21	Methylphenidate – ADHD
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: No new information on prevalence of ADHD after 2019 EML Application has given a long list of studies indicating the public health consequences of ADHD- But (1) without evidence of prevalence, significance of consequences cannot be assessed (2) In all these studies (I read few of them), diagnosis of ADHD was not constant and had overlaps with other psychiatric illnesses (3) Main reference is based on a consensus document which has not been published yet – Not sure about the CoIs in that Consensus document - It is compiled by the World Federation of Attention Deficit Hyperactivity Disorder, the organization which has submitted this application
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.	There is no medicines for ADHD in the EMLs Other medicines in the market (BNF-C, 2017-2018) 1. Atomoxetine- NICE TA 98 (2018) - Limited evidence on comparison with MPH: Studies are graded as low quality (subjective outcomes, open-label, etc.)- No difference in one study 2. Dexamfetamine- NICE TA 98 (2018)- Limited evidence on comparison with MPH: Equal (efficacy and AE) 3. Amphetamine See summary given under evidence of efficacy
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). 1. Application was submitted in 2019 as well 2. In 2019, 2015 Cochrane review{Storebø et al. (2015)} was one of the evidence used in assessing the application: *1. All the trials had high risk of bias, primarily as a result of vested interest, lack of blinding of participants, lack of outcome assessor blinding, selective outcome reporting, or selection bias. Some but not all bias risks were present in most studies. The result of the GRADE assessment was "very low quality" owing to high risks of bias and heterogeneity".* The intervention effect was significantly influenced by choice of scale *2.* Beneficial effect of methylphenidate on teacher rated symptoms in 19 parallel group trials (standardised mean difference (SMD) −0.77, n=1698), corresponding to a mean difference of −9.6 points on the ADHD rating scale.

	3. Authors' conclusion was "results <u>suggest</u> that among children and adolescents with a diagnosis of ADHD, methylphenidate may improve teacher reported symptoms of ADHD and general behaviour and parent reported quality of life. However, given the risk of bias in the included studies, and the very low quality of outcomes, <u>the magnitude of the effects is uncertain"</u> 3. Current application claims" However, relying on the Storebø et al. (2015) meta-analysis is problematic for several reasons. That meta-analysis is flawed due to its use of idiosyncratic methods to assess the quality of the evidence and factual errors, such as inappropriate study 7 inclusion, incorrect downgrading of the evidence based on the GRADE system, and incorrect data imputation. For further details, see Banaschewski et al. (2016) and Hoekstra et al. (2016)" 4. Banaschewski et al. (2016) was a response to the Cochrane review questioning the conclusion in the Cochrane review that the status of the evidence is uncertain is misplaced. Cochrane review authors have responded "Clinical experience seems to suggest that there are people who benefit from this medication. Our systematic review does, however, raise questions regarding the overall quality of the methylphenidate trials. Our systematic review does, however, raise questions regarding the overall quality of the methylphenidate trials. 5. First author of the above comment is an author of this application 6. Hoekstra et al. (2016)" is an Editorial in Eu J Psychiatry: Pointing out 2 inaccuracies mainly "authors failed to mention about 3% of studies without high risk of bias in abstract" and "authors' claim about "lack of blinding". The Editorial has also questioned the authors ideology that "by definition reports that have been sponsored by industry and/or co-authored by experts from industry or experts with declaration of interests are untrustworthy" *7.* Current application has provided Cortese et al.'s meta-analysis (2018): Interpretation: *"Our findings represent the most comprehensive available evidence base to inform patients, families, clinicians, guideline developers, and policymakers on the choice of ADHD medications across age groups. Taking into account both efficacy and safety, evidence from* ***this meta-analysis supports methylphenidate in children and adolescents, <u>and amphetamines in adults, as</u> preferred first-choice medications for the short-term treatment of ADHD.*** *New research should be funded urgently to assess long-term effects of these drugs"* 8. Two authors of above NMA are authors of the current application 9. Crucial points about this NMA: a. "Unlike previous network meta-analyses of ADHD treatments, we have included unpublished data, which were gathered systematically from study authors, the websites of regulatory agencies, and drug manufacturers, using a common set of inclusion criteria for trials in children, adolescents, and adults" <u>– this has both positive and negative aspects</u> b. "Amphetamine is shown as preferred choice over MPH and other medicines in adult". <u>But the application is for including MPH for adult EML as well</u> c. "Medications for ADHD were less efficacious and less well tolerated in adults than in children and adolescents". <u>But the application is for children, adults, adolescents</u> d. The paucity of trials with randomized outcomes beyond 12 weeks highlights the need to fund studies to assess long-term effects of these drugs. e. The risk of bias was rated overall **low in 23·5%** of studies in children and adolescents, unclear in 65·4%, and high in 11·1%. The risk of bias was overall **low in 27·5%** of studies in adults, unclear in 56·8%, and high in 15·7% f. Lowest age group of children in most of the included studies in 5 years – Application has not given any age restriction

	g. Accounting for all included outcomes, our results support methylphenidate in children and adolescents, **and amphetamines in adults**, as the first pharmacological choice for ADHD h. In fact, in adults, amphetamines were not only the most efficacious compounds, as rated by clinicians and by self-report, but also as well tolerated as methylphenidate and the only compounds with better acceptability than placebo. In children and adolescents, even though amphetamines were marginally superior to methylphenidate according to clinicians' ratings, methylphenidate was the only compound with better acceptability than placebo and, unlike amphetamines, was not worse than placebo in terms of tolerability 10. Summary of results from this NMA **For ADHD** Children and adolescents- Efficacy 1. Core symptoms rated by clinicians in children and adolescents closest to 12 weeks, all included drugs were superior to placebo (e.g., SMD –1·02, 95% CI –1·19 to –0·85 for amphetamines, –0·78, –0·93 to –0·62 for methylphenidate, –0·56, –0·66 to –0·45 for Atomoxetine). 2. By contrast, for available comparisons based on teachers' ratings, only methylphenidate (SMD –0·82, 95% CI –1·16 to –0·48) and modafinil (–0·76, –1·15 to –0·37) were more efficacious than placebo. Adults - Efficacy 1. In adults (clinicians' ratings), amphetamines (SMD –0·79, 95% CI –0·99 to –0·58), methylphenidate (–0·49, –0·64 to –0·35), bupropion (–0·46, –0·85 to –0·07), and atomoxetine (–0·45, –0·58 to –0·32), but not modafinil (0·16, –0·28 to 0·59), were better than placebo. With respect to tolerability 1. Amphetamines were inferior to placebo in both children and adolescents (odds ratio [OR] 2·30, 95% CI 1·36–3·89) and adults (3·26, 1·54–6·92); 2. Guanfacine was inferior to placebo in children and adolescents only (2·64, 1·20–5·81); 3. Atomoxetine (2·33, 1·28–4·25), methylphenidate (2·39, 1·40–4·08), and modafinil (4·01, 1·42–11·33) were less well tolerated than placebo in adults only. In head-to-head comparisons, *Only differences in efficacy (clinicians' ratings) were found, favoring amphetamines over modafinil, atomoxetine, and methylphenidate in both children and adolescents (SMDs –0·46 to –0·24) and adults (–0·94 to –0·29)* Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients) No (children < 5 years- no data) MPH should be avoided in females of child bearing age
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes to both sub questions ☐ No ☐ Not applicable Comments: RCTs are not a good tool for assessing adverse effects since large sample is required to identify AE. Tolerability **proportion of patients who dropped out of studies because of side-effects** is different from adverse effects. Hence AEs given in NICE 2018 guidance have to be considered and frequently monitored Changes in height velocity, weight, cardiovascular AE including changes in HR, BP, Substrate abuse,
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Uncertain Effects reported from the 2018 NMA- Evidence for efficacy is inconclusive (see the points below) with risk of bias rates as high or unclear in substantial proportion of studies (Children and adolescents- 76.5%, Adults – 72.5%) 1. Children and Adolescents: Standardized mean difference of -0.78 (–0·93 to –0·62) compared to placebo (clinician rated outcome measures) {inferior to amphetamine} 2. Children and Adolescents: Standardized mean difference of -0.82 (–1·16 to –0·48) compared to placebo (teacher rated outcome measures {no data for amphetamine} 3. Adults: Standardized mean difference of –0·49 (–0·64 to –0·35) compared to placebo (clinician rated outcome measures) {inferior to amphetamine Lack of data after 12 weeks Lack of data in children < 5 years Adverse effects of concern First line of therapy for ADHS is non pharmacological
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Low
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: 1. To be diagnosed by specialists 2. First level non-pharmacological interventions to be provided by specialist 3. Monitoring for AEs
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:

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:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	1. Not an expensive medicine 2. Wide availability has the potential to distract the focus from non-pharmacological first line intervention 3. Modified release is encouraged, however, some brands of modified release preparations have failed to show bioequivalence. Developing countries will not be procuring the innovator brand
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.	**NOT RECOMMENDED** Additional data of importance is from the 2018 NMA – Results and conclusion of this NMA did not provide convincing evidence to change the decision taken in 2019 I have given my comments on this NMA under several sections above, So I have not repeated them here again
References (if required)	1. Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A.J., Carucci, S., Atkinson, L.Z., Tessari, L., Banaschewski, T., Coghill, D., Hollis, C., Simonoff, E., Zuddas, A., Barbui, C., Purgato, M., Steinhausen, H.C., Shokraneh, F., Xia, J., Cipriani, A., 2018. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 5, 727-738 TRS 2. Storebo, O.J., Krogh, H.B., Ramstad, E., Moreira-Maia, C.R., Holmskov, M., Skoog, M., Nilausen, T.D., Magnusson, F.L., Zwi, M., Gillies, D., Rosendal, S., Groth, C., Rasmussen, K.B., Gauci, D., Kirubakaran, R., Forsbol, B., Simonsen, E., Gluud, C., 2015. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. Bmj 351, h5203. NICE 3. 2019-TRS (WH0) 4. NICE- TA 98