2019 Expert Committee on Selection and Use of Essential Medicines

Peer Review Report

Methylphenidate – Addition

(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☐ No ☑

1. No adult data
2. Children data - Until 2010
3. In the 2010 – Authors have noticed that “prevalence remained stable over time” (1990-2010) - Will it be same for 2010- 2020?
4. 2007 systematic review and metaregression study (1): No data for adults (subgroup analysis is available for children and adolescents – prevalence is very much higher in children)
5. While accepting the public health need of the medicine in children, I am unable to find evidence from the application for the public health need of this medicine in adults in term of prevalence data

“Reference 11 and 12 in the application: For children aged 5–19 years, the global pooled prevalence of ADHD in 2010 was 2.2% (2.0–2.3) and 0.7% (0.6–0.7) for males and females, respectively. ADHD prevalence in 1990 and 2005 (Both years: Males: 2.2%, 2.0–2.3; Females: 0.7%, 0.6–0.7) was almost identical to 2010, indicating that prevalence remained stable over time”.

2007 Reference (not given in the application): One hundred and two studies comprising 171,756 subjects from all world regions were included. The ADHD/HD worldwide-pooled prevalence was 5.29%. Geographic location was associated with significant variability only between estimates from North America and both Africa and the Middle East. No significant differences were found between Europe and North America

(2) Have all important studies/evidence of which you are aware been included in the application?

Yes ☑ No ☐

Please provide brief comments on any relevant studies that have not been included:
NA

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☐ No ☐
(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

1. Majority of studies are limited to children and adolescents only (though the upper limit for the adolescent age group differs from study to study). Applicant has done a detailed systematic review in December 2018 and has selected 29 studies and review articles to extract the evidence. Though the application did not provide a list of these selected publications within the text, I managed to get the details from the reference list (Reference 26- reference 53): Of them 23 papers (26-48) were on children and adolescents and 5 were on adults (49-53).

2. Majority of studies were small sample sized with a wide range of indicators for outcome assessment and the 15 published reviews had many limitations (2)

3. Cochrane review (2)
   a. “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
   b. 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.
   c. Authors’ conclusion was “results suggest 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, the magnitude of the effects is uncertain”

4. I read with interest the Cochrane review on efficacy of MPH in adults with ADHD, subsequent criticisms on the review and final decision of the Cochrane to withdraw the review (3,4). In the absence of any major papers favoring MPH after the “withdrawn review”, I consider that the evidence for adults is inconclusive

5. There is a meta-analysis published in 2018. MPH was less efficacious than LDX. Also, “Significant heterogeneity was observed among the studies of MPH in the assessment of CGI and the retention in treatment (acceptability)”

6. To conclude, the beneficial effect is symptom control in children and adolescents with ADHD- but the evidence is of very low quality (means “We are very uncertain about the estimate”)

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

   No, however diverse settings is limited in this instance
Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ✔️ (for both questions)  No ☐

1. Application has discussed the safety and adverse effects adequately
2. However, most of the evidence (not all) come from the studies which have been used to discuss efficacy (limitations – very low and low quality evidence, etc). Please note that compared to efficacy outcomes, safety outcomes need large number of patients. Primary outcome in most of these studies was efficacy endpoints.
3. There are additional studies as well in the application addressing the adverse effects, discontinuation, etc. Some are of very low quality evidence (it is commented in the application itself)
4. At the end the application concludes, that “Thus, while cardiovascular events, growth inhibition, or tics generally may not be of major concern, there are common adverse events associated with MPH use that include abdominal pain, decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, decreased weight, irritability, and hyperhidrosis”
5. Reference 75 and 76 are used to “exclude” effects on growth from list of significant AE of MPH that requires monitoring
   a. Reference 75 is a case-control study to observe height and weight in children with ADHD (treatment effects is a subgroup analysis with just 110 children with mean age of starting treatment is 8.7 in males and 8.4 in females. Conclusion was “There were no significant associations between duration of stimulant treatment and any growth outcomes in the combined sample of male and female subjects, adjusting for sex (all p values >0.05)” – I would exercise extreme caution in using this results to “exclude” growth monitoring from a child who is on MPH.
   b. Reference 76: Authors have concluded “Treatment with stimulants in childhood modestly reduced expected height and weight. Although these effects attenuate over time and some data suggest that ultimate adult growth parameters are not affected, more work is needed to clarify the effects of continuous treatment from childhood to adulthood. Although physicians should monitor height, deficits in height and weight do not appear to be a clinical concern for most children treated with stimulants”. Editorial on the same issue on this study has highlighted many issues the authors did not consider or could not consider because the original studies lacked the data. Subsequently there was another letter to editor commenting on the interpretation. Authors also have disclosed acceptance of financial contribution from pharmaceutical industries. Hence, I will not recommend using this evidence to remove “growth monitoring” for children on MPH.
6. References (71–74) are used to “exclude” effects on cardiovascular system from list of significant AE of MPH that requires monitoring
   a. Reference 71: Children and adolescents: Retrospective cohort large scale study: End point studied was serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke) and conclusion
was “This large study showed no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events, although the upper limit of the 95% confidence interval indicated that a doubling of the risk could not be ruled out. However, the absolute magnitude of such an increased risk would be low”

b. Reference 72: Same research group as above, but on adults. Same end points. Less person years than the above study. Conclusion – “Among young and middle-aged adults, current or new use of ADHD medications, compared with non-use or remote use, was not associated with an increased risk of serious cardiovascular events”

c. Reference 73: End points were emergency department or inpatient diagnosis of angina pectoris, cardiac dysrhythmia, or transient cerebral ischemia (cardiac events) or 2) tachycardia, palpitations, or syncope (cardiac symptoms). Authors have disclosed accepting contributions from Pharmaceutical industries.

7. Evidence is not adequate to remove blood pressure monitoring from patients on MPH – Given as common or very common adverse effect in BNFc which require 6 monthly monitoring (and also by FDA)

8. Problem of substrate abuse cannot be overlooked – Very significant and outweigh the benefit in countries which have weak regulatory mechanisms

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Uncertain (based on lack of high quality evidence on effectiveness and important adverse effects)
ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?
   Yes ☑ No □

1. Diagnosis needs specialist on child / adolescent/ adult Psychiatrist
2. Monitoring (growth, BP) need regular follow up
3. Prevention of substrate abuse (by the individual/ family members) or malingering the symptoms by a non-patient need careful diagnosis and follow up

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)
   Yes □ No ☑

However, there had been changes in the regulations and policies especially by the FDA and Health Canada, mainly based on risk of serious cardiovascular events in the past. Most of them have been changed after reports from advisory committees and epidemiological studies.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?
   Yes □ No □

Please provide brief details:

(9) Please comment briefly on issues regarding cost and affordability of this medicine.
Acceptable cost and affordability, but effectiveness is not supported by high quality evidence

(10) Any additional comments?

Though application is for IR, ensuring that all prescribers will stick to IR is going to be difficult in many developing countries. There could be automatic assumption that IR and MR are same except in frequency of administration. However, when it comes to MR, some brands have failed to show bioequivalence. Developing countries will not be procuring the innovator brand.

(11) Please frame the decisions and recommendations that the Expert Committee could make.
Not recommended

(12) **References** (if required)