I.14 (item number)	Simvastatin - polycystic ovary syndrome (application title)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: PCOS is the most common endocrinopathy affecting 8-13% reproductive-aged women in the world. It is a leading cause of infertility, and its symptoms could substantially reduce quality of life, affect neuropsychological status, increased risk of depression and adverse health outcomes related to metabolic dysfunction and cardiovascular diseases as well as burden to health care cost.
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.	Simvastatin is a lipid lowering agent currently listed in the EML with indication for hyperlipidemia and coronary atherosclerosis treatment. The application is for adding a new indication for the use of the medication in the eml. Currently, no other medication is listed in the eml for treatment of PCOS.
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 evidence included 5 systematic reviews the most recent is 2020. The SRs includes one Cochrane Systematic Review (Raval et al, 2011) which concluded that "Although statins improve lipid profiles and reduce testosterone levels in women with PCOS, there is no evidence that statins improve resumption of menstrual regularity or spontaneous ovulation, nor is there any improvement

	of hirsutism or acne. There is a need for further research to be performed with large sample sizes and well-designed RCTs to assess clinical outcomes." The most recent network meta-analysis (Almalki et al, 2020) only evaluated the effect of statins on testosterone level (not on clinical outcomes) and reported no significant difference on the reduction of testosterone level between simvastatin vs other treatment modalities (metformin, combined oral contraceptives, lifestyle modification, & placebo). Other meta-analyses also assessed laboratory outcomes (dehydroepiandrosterone-DHEA, total testosterone, TC, TG and LDL) and involved a small number of RCTs) and suggested that "a large-scale, randomized controlled study is needed to ascertain this uncertainty". Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Unclear
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Statins are widely used for its present indications (hyperlipidemia and coronary atherosclerosis) and considered as safe.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Many women with PCOS seek treatment due to infertility, while statins is contraindicated in pregnancy
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Current evidence still shows high uncertainty with regard to the risk and benefit of statins for PCOS treatment

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Moderate quality of evidence. Although there are already 5 SRs (including one Cochrane SR), it involves small number of RCTs with small sample size. Moreover, currently there is also no evidence-based clinical practice guidelines recommending it.
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:
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: It has been approved and marketed globally for current indication.
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: Also not stated in the recommendation of any evidence-based clinical practice guidelines from relevant professional organizations.

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	As simvastatin is currently widely use globally, I believe there would be no important issues regarding its access, cost and affordability.
Any additional comments	
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.	I do not recommend the addition of new indication for simvastatin, as the evidence for its effectiveness is still limited.
References (if required)	Raval AD, Hunter T, Stuckey B, Hart RJ. Statins for women with polycystic ovary syndrome not actively trying to conceive. Cochrane Database Syst Rev [Internet]. 2011 [cited 2020 Jun 23];(10). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008565.pub2/full Almalki HH, Alshibani TM, Alhifany AA, Almohammed OA. Comparative efficacy of statins, metformin, spironolactone and combined oral contraceptives in reducing testosterone levels in women with polycystic ovary syndrome: a network meta-analysis of randomized clinical trials. BMC Womens Health. 2020 Apr 5;20(1):68. Yang S, Gu Y-Y, Jing F, Yu C-X, Guan Q-B. The Effect of Statins on Levels of Dehydroepiandrosterone (DHEA) in Women with Polycystic Ovary Syndrome: A

	Systematic Review and Meta-Analysis. Med Sci Monit Int Med J Exp Clin Res. 2019 Jan 20;25:590–7. Gao L, Zhao F-L, Li S-C. Statin is a reasonpollable treatment option for patients with Polycystic Ovary Syndrome: a meta-analysis of randomized controlled trials. Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc. 2012 Jun;120(6):367–75.