

I.14	Simvastatin – polycystic ovary syndrome (PCOS)
Does the application adequately address the issue of the public health need for the medicine?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: PCOS is the most common endocrinopathy affecting reproductive-aged women worldwide. Prevalence is 8-13, but it can go up to 20% due to the differences in diagnostic criteria. PCOS is associated with metabolic syndrome, infertility, obesity, hypertension, type 2 diabetes, cardiovascular disease and some gynaecological cancers. This highlights the need of appropriate treatment.
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.	Metformin is an option for the treatment of PCOS already included in the EML as an oral hypoglycaemic agent. Simvastatin targets a different aspect of the metabolic disturbances that affect patients with PCOS.
Have all important studies and all relevant evidence been included in the application?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> 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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> 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). Most of the studies showed only benefits in surrogate outcomes (testosterone level, DHEA-S, androstenedione, lipid profile) and no evidence of improvement in patient important outcomes such as menstrual regularity, ovulation and fertility, hirsutism, acne or BMI. Also, 2 systematic reviews showed superiority of atorvastatin over simvastatin. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

2021 Expert Committee on Selection and Use of Essential Medicines
Application review

<p>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>All the included studies reported that simvastatin was well tolerated. Additionally, the side effects of this drug are really well known since it is frequently used worldwide for hyperlipidaemias.</p>
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Simvastatin is rarely associated with severe side effects such as immune-mediated myopathy and severe myopathy. In general they are safe and well tolerated.</p>
<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<p>Unclear. Simvastatin is a safe and affordable drug but its effects on clinical criteria and long term outcomes hasn't been adequately demonstrated.</p>
<p>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</p>	<p>The quality of the available evidence is moderate.</p>
<p>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)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>
<p>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)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>

2021 Expert Committee on Selection and Use of Essential Medicines
Application review

<p>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)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Yes, it is included in “Prevention and Control of Non-communicable Diseases: Guidelines for primary health care in low resource settings”</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>Simvastatin is available around the world as a generic from multiple manufacturers. In most countries it is usually affordable.</p>
<p>Any additional comments</p>	
<p>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.</p>	<p>Even when the available evidence shows that simvastatin can improve biochemical markers in patients with PCOS this does not seem to reflect into clinical benefit according to the available evidence. I think that trials with a large sample size and longer follow up are needed in order to evaluate these outcomes.</p> <p>Also, available evidence seems to suggest a possible superiority of atorvastatin. This also needs to be clarified.</p>
<p>References (if required)</p>	