

A.38	Varenicline – smoking cessation
Does the application adequately address the issue of the public health need for the medicine?	<p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable </p> <p>Comments: Smoking is a major public health threat worldwide and causes substantial health and economic harm. There is sufficient evidence that smoking has a causal relationship with cancers. Promoting smoking cessation will significantly improve the health of smokers, their close relations, and will save enormous financial expenses for both high- and low-income settings.</p>
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.	<p>Varenicline is being proposed as an aid for smoking cessation. The model list does not currently contain any agent for smoking cessation to the best of my knowledge. Varenicline has proven efficacy for smoking cessation from several clinical evaluations including RCTs with synthesized evidence suggesting effectiveness considering over hundred studies from diverse settings. It is also well tolerated and cost-effective.</p> <p>The application considers efficacy and tolerability in diverse sets of users including psychiatric and non-psychiatric users, co-morbidity, adolescents etc.</p> <p>The application additionally considers cessation maintenance.</p> <p>Existing studies have compared varenicline, versus bupropion, NRT, placebo, nortriptyline, and gabapentin. Varenicline is superior to other drugs (including Bupropion) in smoking cessation and adverse effects.</p>
Have all important studies and all relevant evidence been included in the application?	<p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable </p> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p>

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

<p>Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>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).</p> <ol style="list-style-type: none"> 1. Efficacy for smoking cessation: The pooled RR for continuous or sustained abstinence at six months or longer for varenicline at standard dosage versus placebo was 2.24 (95% CI 2.06 to 2.43; 27 trials, 12,625 people; <i>high-quality evidence</i>). Varenicline at lower or variable doses was also shown to be effective, with an RR of 2.08 (95% CI 1.56 to 2.78; 4 trials, 1266 people). The pooled RR for varenicline versus bupropion at six months was 1.39 (95% CI 1.25 to 1.54; 5 trials, 5877 people; <i>high-quality evidence</i>). The RR for varenicline versus NRT for abstinence at 24 weeks was 1.25 (95% CI 1.14 to 1.37; 8 trials, 6264 people; <i>moderate-quality evidence</i>). (Cahill 2016) 2. Tolerability and safety: The most reported adverse effect of varenicline was nausea, which was mostly at mild to moderate levels and usually subsided over time. Latest evidence does not support a link between varenicline and these disorders, although people with past or current psychiatric illness may be at slightly higher risk. 3. Cost: <p>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?</p> <p>Yes, there is evidence from several countries including high to low income countries; diverse patients groups and ages; co-morbidities etc</p>
<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>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>A synthesis of existing evidence suggest main side effects is nausea and that suicidal ideation did not seem related to treatment</p>
<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<p>Favourable: the risks associated with the agent is far less than that associated with smoking. SAEs are rare with no reported deaths related to treatment. However, psychiatric outcomes must be closely monitored.</p>

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

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	High: there is high-certainty evidence that varenicline can aid in smoking cessation compared to all other existing agents, and further research on the topic may not provide any additional evidence that will change recommendations.
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)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: Yes, I propose the need to monitor users considering the risks of mental and behavioural issues reported in studies. Healthcare workers need to be trained in identification and monitoring of such adverse effects.
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)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> 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)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Smoking cessation interventions are among the most cost-effective public health interventions. There is insufficient evidence on affordability of varenicline for smoking cessation although nor for LMICs.
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.	<p>Considering the body of evidence in support of efficacy and tolerability of varenicline, this agent is effective and safe for smoking cessation. However, considering limited evidence on affordability in LMICs there is need for the expert committee to set up mechanisms for such estimations with ministries of health in LMICs. Also considering the possible mental health adverse effects, clinicians training for monitoring and managing potential mental and behavioural issues must be considered.</p> <p>Mindful of all the above, I recommend the inclusion of varenicline in the EML.</p>
References (if required)	Howes, Seth, et al. "Antidepressants for smoking cessation." <i>Cochrane Database of Systematic Reviews</i> 4 (2020).