A.5	Bupropion – smoking cessation
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable 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.
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.	Bupropion 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. Bupropion has proven efficacy for smoking cessation from several clinical evaluations including RCTs with synthesized evidence from Cochrane database suggesting effectiveness considering over hundred studies from diverse settings. It is also well tolerated and cost-effective. The application considers efficacy and tolerability in diverse sets of users including psychiatric and non-psychiatric users, co-morbidity, adolescents etc. Existing studies have compared bupropion to NRT, placebo, varenicline, nortriptyline, and gabapentin.
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. Efficacy for smoking cessation: There is high-certainty evidence that bupropion increased long-term smoking cessation rates (RR 1.64, 95% CI 1.52 to 1.77; I2 = 15%; 45 studies, 17,866 participants) as reported in a Cochrane review with 100+ studies. A meta-analysis of six studies provided evidence that bupropion resulted in inferior smoking cessation rates to varenicline (RR 0.71, 95% CI 0.64 to 0.79; I2 = 0%; 6 studies, 6286 participants) 2. Tolerability and safety: there is high-certainty evidence that use of bupropion

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<tr><td></td><td>resulted in more trial dropouts due to adverse events of the drug than placebo (RR 1.37, 95% CI 1.21 to 1.56; I2 = 19%; 25 studies, 12,340 participants). Participants randomized to bupropion were also more likely to report psychiatric AEs compared with those randomized to placebo (RR 1.25, 95% CI 1.15 to 1.37; I = 15%; 6 studies, 4439 participants).

3. Cost: there are reported cost benefits with bupropion including a 3000+ cost per QALY gained

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

Yes, there is evidence from several countries including high to low income countries; diverse patients groups and ages; co-morbidities etc</td></tr>
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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 ☐ No ☐ Not applicable Comments: A synthesis of existing evidence suggest increased unwanted effects, particularly those relating to mental health, and that unwanted effects may increase the chance that people stop using the medicine.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable: Using the antidepressant, bupropion, makes it 52% to 77% more likely that a person will successfully stop smoking, which is equal to five to seven more people successfully quitting for six months or more for every hundred people who try to quit. Although there are side effects that must be considered, including mental health issues, considering the positive impact of smoking cessation I believe the benefits outweighs the risks.
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 bupropion can aid in smoking cessation (although inferior to varenicline), 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)	☒ Yes ☐ No ☐ 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)	☐ 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.	Smoking cessation interventions are among the most cost-effective public health interventions. There is sufficient evidence on affordability of bupropion 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.	Considering the body of evidence in support of efficacy and tolerability of bupropion, this agent is promising 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. Mindful of all the above, I recommend the inclusion of Bupropion in the EML.
References (if required)	Howes, Seth, et al. "Antidepressants for smoking cessation." *Cochrane Database of Systematic Reviews* 4 (2020).