A.5 (item number)	**Bupropion - smoking cessation** (application title)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Tobacco epidemic is a global problem with serious public health consequences. Tobacco consumption and exposure to tobacco smoke have devastating effects to health, social economic and environment. Scientific evidence has unequivocally established that tobacco consumption and exposure to tobacco smoke cause death, disease and disability (WHO FCTC, 2003)
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.	Accessibility and affordability for treatment of tobacco dependence including pharmaceutical products should be facilitated (WHO FCTC, 2003). A study which assessed 61 national tobacco cessation and treatment guidelines found that most recommended smoking cessation measures were Nicotine Replacement Therapy (NRT), bupropion and varenicline. (Nilan K et al. 2018) NRT is currently the only treatment option for smoking cessation (nicotine dependence) included on the WHO Model List of Essential Medicines. Bupropion SR may be used in combination with nicotine replacement therapy (NRT).
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 application already included a 2020 updated Cochrane SR which concluded that there is high-certainty evidence that bupropion increased long-term smoking cessation rates. The SR included 45 clinical trials (Howes S et al, 2020) *Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?* There is still lack of RCTs on tobacco cessation in LMIC; most RCTs were psychosocial, with limited behavioral and pharmacological variants – 6 studies on bupropion (4 show positive change in outcome of interest, 2 show no change compare to without bupropion) (Kumar et al, 2021). Beneficial effects were similarly observed among elderly population, adolescents, smokers with COPD or CVD or psychiatric disorders. Positive but insignificant difference was observed among smokers with depression. Its safety/effectiveness among children has not been established.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Safety among pregnant and lactation women, elderly, people with impaired renal function, impaired hepatic function, smokers with COPD, CVD, depression, psychiatric disorders have been established. Safety among children has not been established. Bupropion SR is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: A 2020 Cochrane SR reported an increased risk of insomnia and anxiety, as well as psychiatric adverse events of any severity.

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable The benefit of smoking cessation which will reduce its long-term effect on health, socio-economic and environment clearly outweigh the risk of adverse events due to pharmacologic intervention.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of the evidence is high as it includes an updated Cochrane Systematic Review with a good number of RCTs.
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: No specialist training is required for the prescription or use of the medicine. However, the success of medications for quitting smoking is optimized when patients are prepared to quit and receive quit advice, counseling, and support from health care providers.
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: By the end of 2018, bupropion was available in 98 countries.

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: Medications that have been clearly shown by scientific evidence to increase the chances of tobacco cessation should be made available to tobacco users wanting to quit and where possible be provided free or at an affordable cost. (WHO FCTC Guidelines for implementation, 2013) Bupropion together with Veranicline was stated as non-nicotine pharmacological intervention to help people to quit smoking in the WHO Report on the Global Tobacco Epidemic 2019.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Although not part of the WHO best buys for NCDs, evidence from several systematic reviews and cost-effectiveness studies supports bupropion as a cost-effective medication when considering the costs of treatment compared to the resulting benefits in terms of avoided mortality, morbidity, and the costs of care for smoking-related diseases. However, evidence on its cost-effectiveness in LMICs are still limited.
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.	The evidence for inclusion of bupropion in the list is strong, however, the evidence on its use and availability in LMIC is still limited. The effectiveness of it is also highly relied on behavioural education approach like counselling and in many countries especially the LMIC this approach is yet to be optimized together with the strengthening of the policy against tobacco. Considering that, the urgency of including bupropion in the model list is currently low.

References (if required)	World Health Organization. WHO Framework Convention on Tobacco Control Geneva: World Health Organization; 2003. Nilan K, McNeill A, Murray RL, McKeever TM, Raw M. A survey of tobacco dependence treatment guidelines content in 61 countries. Addiction. 2018;113(8):1499-506. Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2020;4(4):Cd000031 Kumar, N., Ainooson, J., Billings, A. et al. The scope of tobacco cessation randomized controlled trials in low- to middle-income countries: protocol for a scoping review. Syst Rev 9, 86 (2020). https://doi.org/10.1186/s13643-020-01361-2