F.8	Ethinylestradiol/Etonogestrel Vaginal Ring - contraception
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Unintended pregnancy is regarded as a serious public health issue both in developed and developing countries and has received growing research and policy attention during last few decades . It is a major global concern due to its association with adverse physical, mental, social and economic outcomes
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.	The application is for Contraceptive Vaginal Rings (CVR) containing Ethinylestradiol/Etonogestrel. The main advantages of CVRs are their effectiveness (similar or slightly better than the pill), ease of use without the need of remembering a daily routine, user ability to control initiation and discontinuation, nearly constant release rate allowing for lower doses, greater bioavailability and good cycle control with the combined ring, in comparison with oral contraceptives.
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: Most of the studies cited on CVRs have been conducted in North America, Europe and South-East Asia. In sub-Saharan Africa where the public health problem of unwanted pregnancy is highest, few studies on CVRs have been cited.
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). Evidence provided shows that CVR offer an effective contraceptive option, expanding the available choices of hormonal contraception. The main advantages of CVRs are their effectiveness (similar or slightly better than the pill), ease of use without the need of remembering a daily routine, user ability to control initiation and discontinuation, nearly constant release rate allowing for lower doses, greater bioavailability and good cycle control with the combined ring, in comparison with oral contraceptives. The ring's effectiveness is similar to other combined hormonal contraceptive methods, with pregnancy rates less than 1% in large efficacy trials. Increased effectiveness may result from ease of use and the minimal user intervention required Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No. Little evidence has

	been cited from Sub-Saharan Africa
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: Specifically related with safety, the application provides different references in Literature that offer information related to exposure to Ethinylestradiol/Etonogestrel combined contraceptive vaginal ring. Those references have shown that the use of the vaginal ring was not found to significantly affect blood pressure. No clinically relevant change from baseline was seen during observational trials or postmarketing surveillance in either diastolic or systolic blood pressure. In a trial comparing COC and Ethinylestradiol/Etonogestrel combined contraceptive vaginal ring use, ≤ 4% of subjects in each treatment group experienced hypertension. No significant changes in cervical cytology have been attributed to Ethinylestradiol/Etonogestrel combined contraceptive vaginal ring use . The most frequently reported undesirable effects in the clinical trials with a Ethinylestradiol/Etonogestrel combined contraceptive vaginal ring were headache and vaginal infections and vaginal discharge, each reported by 5-6% of the women. However, non of the studies cited were undertaken in sub-Saharan Africa, hence these results cannot be extrapolated to that region.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: The application lists several conditions where use of CVR containing Ethinylestradiol/Etonogestrel is contraindicated. In addition, thrombotic and thrombolytic events associated with combined hormonal contraceptives would be cause for concern in resource-poor settings.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The benefit to risk ratio is “moderate”.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The quality of evidence is low
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: However, associated cardiovascular adverse effects would need monitoring
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.	Only one study on cost effectiveness is quoted by the applicants. No studies in resource-poor settings are provided in the application
Any additional comments	None
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 have concerns about adverse drug effects associated with combined hormonal contraceptives, and the challenge these would pose in terms of monitoring especially in resource-poor settings such as in most sub-Saharan African facilities. I also have concerns about limited studies that have been conducted in this region on the effects (adverse and beneficial) of CVRs. I, therefore recommend the committee NOT to support this application
References (if required)	