

<b>F.8</b> (item number)	<b>Ethinylestradiol + etonogestrel – Contraception</b> (application title)
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: <i>Unintended pregnancy is a serious public health issue, associated with adverse physical, mental, social and economic outcomes. Modern methods of contraception have an important role in preventing unintended pregnancies. Still, the adherence to the many alternatives is compromised due to the woman's health concerns by the patient, side effects or inconvenience of use.</i>
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.	<i>There are several contraceptives in the EML, including the following presentation formats: oral hormonal, injectable hormonal, intrauterine devices, barrier methods, implantable, and intravaginal hormone devices. The ethinylestradiol + etonogestrel vaginal ring would be used as an alternative to those methods or an adjuvant.</i>
Have all important studies and all relevant evidence been included in the application?	<input type="checkbox"/> Yes <input checked="" 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: <i>A Cochrane Systematic Review [Lopez 2013] was not included in the application. This review included 11 RCTs and only 4 of them were reported on the application. Another systematic review [Lopez-Picado 2017] including 14 randomized clinical trials was also not included.</i>
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). <i>A systematic review [Lopez-Picado 2017], including 14 randomized clinical trials (RCTs), assessing contraceptive vaginal ring (CVR) with ethinylestradiol + etonogestrel versus oral hormone contraceptive (OHC) concluded that:</i> <ul style="list-style-type: none"> <li><i>CVR may slightly reduce or have no effect on the risk of pregnancy (Peto OR: 0.52 [95% CI: 0.26-1.04; 10 RCT; 246 participants; <math>I^2 = 0\%</math>])</i></li> <li><i>CVR may reduce the presence of nausea (Peto OR: 0.66 [95% CI: 0.46-0.93]).</i></li> <li><i>CVR may reduce the risk of breakthrough bleeding during the use (Peto OR: 0.68 [95% CI: 0.51-0.91]).</i></li> <li><i>CVR may reduce, increase or even have no effect on compliance rate (Peto OR 0.99; 95% CI 0.33–2.94)</i></li> <li><i>CVR may reduce, increase or even have no effect on the risk of withdrawal bleeding in the hormone free interval (Peto OR: 0.81; 95% CI 0.44–1.49).</i></li> </ul>

	<ul style="list-style-type: none"> <li>• CVR may reduce, increase or even have no effect on the risk of headache as a side effect (Peto OR 1.09; 95% CI: 0.88–1.34).</li> <li>• Serious adverse events (as thrombosis and cardiovascular events) were not considered by the review authors.</li> <li>• GRADE was not performed to assess the evidence certainty, reasonable to expect that the evidence could be downgraded due to methodological limitations, inconsistency and imprecision for most of outcomes).</li> </ul> <p><i>The evidence presented by the applicant is limited about the comparative efficacy and safety of CVR when compared with Injectable hormonal contraceptives, Intrauterine devices, barrier methods and barrier methods.</i></p> <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><i>Subgroup analyses were not performed by the systematic review stated above addressing diverse settings and participants</i></p>
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: <i>The main safety concerns are the same to any ethynilestradiol + etonogestrel contraceptives. Local events are also common (reported by 5~6% of women), including vaginal infection and vaginal discharge.</i></p>
Are there any adverse effects of concern, or that may require special monitoring?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p><i>An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs (combined hormonal contraceptives).</i></p> <p><i>Therefore, in general, this type of contraception should not be recommended for patients with high risk or with a direct personal or familiar history of thromboembolic events.</i></p>
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	<i>The overall benefit to risk ratio is favourable, but the underling quality of the evidence limits this finding.</i>
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	<i>The overall quality of the evidence is probably low or very low due to methodological limitations, inconsistency and imprecision from the available RCT.</i>

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<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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments: <i>The intervention should be promoted only with a health-educational program that will allow the correct use of the vaginal ring. When offered this contraception method, women need to be instructed on the correct use mode.</i></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>
<p>Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: <a href="https://www.who.int/publications/who-guidelines">https://www.who.int/publications/who-guidelines</a>)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>(1) WHO. Medical eligibility criteria for contraceptive use. Available from: <a href="https://www.who.int/publications/i/item/9789241549158">https://www.who.int/publications/i/item/9789241549158</a>.</p> <p><i>"Pending further evidence, the GDG concluded that the evidence available for COCs applies to the combined contraceptive P and CVR, and therefore the P and CVR should have the same categories as COCs. The assigned categories should, therefore, be considered a preliminary, best judgement, which will be re-evaluated as new data become available."</i></p> <p>(2) WHO. Selected practice recommendations for contraceptive use. Third edition 2016. Available from: <a href="http://apps.who.int/iris/bitstream/handle/10665/252267/9789241565400-eng.pdf;jsessionid=95A367725F24E026CC12F5D648B065B5?sequence=1">http://apps.who.int/iris/bitstream/handle/10665/252267/9789241565400-eng.pdf;jsessionid=95A367725F24E026CC12F5D648B065B5?sequence=1</a>.</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p><i>The applicant presented a cost-effectiveness analysis performed at Spain that compared vaginal ring to oral contraception or patch [Guerra 2015], and concluded that vaginal ring is the most cost-effective option.</i></p> <p><i>It is reasonable to expect that ethinylestradiol + etonogestrel vaginal ring is relatively more expensive than other contraception alternatives such as oral contraception with heterogeneous accessibility and affordability in different countries.</i></p>
<p>Any additional comments</p>	<p>----</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><i>The limited confidence on the evidence that ethinylestradiol + etonogestrel vaginal ring is more or equally effective than other contraception methods and the uncertainties regarding its cost and cost-effectiveness in diverse settings prevents a favourable recommendation to include this intervention on the EML.</i></p> <p><i>It is worth to notice that other effective contraception methods are already covered by the list.</i></p> <p><i>Therefore, the proposed recommendation to the Expert Committee is to <b>not incorporate ethinylestradiol + etonogestrel vaginal ring on the EML.</b></i></p>

References (if required)	<p><i>Guerra S, Sánchez F, Encinas A, Ugarte L, Barbadillo N, Lete I. Costes de la anticoncepción hormonal combinada en España: ¿hay algún método más costeefectivo?. Progresos de Obstetricia y Ginecología. 2015; 58(5); 221-226.</i></p> <p><i>Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2013 Apr 30;2013(4):CD003552.</i></p> <p><i>López-Picado A, Lapuente O, Lete I. Efficacy and side-effects profile of the ethinylestradiol and etonogestrel contraceptive vaginal ring: a systematic review and meta-analysis. Eur J Contracept Reprod Health Care. 2017 Apr;22(2):131-146. doi: 10.1080/13625187.2017.1287351. Epub 2017 Feb 14. PMID: 28256919.</i></p>
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