

5.03 ETONOGESTREL with ETHINYLESTRADIOL, Vaginal ring containing etonogestrel 11.7 mg with ethinylestradiol 2.7 mg, NuvaRing[®], Organon Pharma Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Restricted Benefit listing for etonogestrel 11.7 mg with ethinylestradiol 2.7 mg contraceptive vaginal ring (CVR) (NuvaRing[®]) for contraception for women seeking contraception but requiring a non-oral preparation. The submission proposed that the target population would be women who must meet at least one of the following criteria: difficulty swallowing tablets, gastrointestinal disturbances (e.g. malabsorption), or undesirable side effects with oral contraceptives. The ESC considered the criterion ‘undesirable side effects with oral contraceptives’ to be imprecise.
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus depot medroxyprogesterone acetate injection (DMPA).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Women seeking contraception with at least one of the following conditions: <ul style="list-style-type: none"> • Difficulty swallowing pills, • Gastrointestinal disturbances (e.g., malabsorption), • Undesirable side effects with oral contraceptives
Intervention	Etonogestrel 11.7 mg with ethinylestradiol 2.7 mg per vaginal ring (NuvaRing) every 4 weeks
Comparator	DMPA intramuscular injection every 12 weeks
Outcomes	Unintended pregnancy Adverse effects Discontinuation/adherence
Clinical claim	Etonogestrel 11.7 mg with ethinylestradiol 2.7 mg vaginal ring is as effective as DMPA at preventing unintended pregnancies Etonogestrel 11.7 mg with ethinylestradiol 2.7 mg vaginal ring has a similar safety profile to DMPA.

Source: Table 1.1.1, p17 of the submission main body.

DMPA = depot medroxyprogesterone acetate

2 Background

Registration status

- 2.1 NuvaRing was Therapeutic Goods Administration (TGA) registered on 9 July 2008 for use for contraception.

Previous PBAC consideration

- 2.2 The Pharmaceutical Benefits Advisory Committee (PBAC) has not previously considered an application to list CVR.
- 2.3 The submission was made in response to an Inquiry into universal access to reproductive health care undertaken by the Senate Community Affairs Reference Committee. One recommendation from the Report from the inquiry was “...that the Department of Health and Aged Care and the Pharmaceutical Benefits Advisory Council [sic; Committee] work with the pharmaceutical industry to consider options to improve access to a broader range of hormonal contraceptives that are not currently Pharmaceutical Benefits Scheme subsidised, including newer forms of the oral contraceptive pill, the emergency oral contraceptive pills and the vaginal ring” (Recommendation 6).¹
- 2.4 The PBAC held an Oral Contraceptives Stakeholder Meeting in October 2024, to discuss evidence available that may demonstrate the additional benefits of newer oral contraceptives compared to older generation oral contraceptives. It was identified that it is important to have a range of contraceptive options, including non-oral options, so that a woman can choose the most appropriate contraceptive at various points in her life. It was also noted that there are some circumstances in which a CVR may be preferable to combined oral contraceptives (COCs).²

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

3.1 The submission requested the following new listing:

Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ETONOGESTREL + ETHINYLESTRADIOL					
etonogestrel 120 microgram/24 hours + ethinylestradiol 15 microgram/24 hours vaginal drug delivery system, 3 rings	NEW MP NP MW	1	3	3	NuvaRing

¹ The Senate Community Affairs Reference Committee, (2023), ‘Ending the postcode lottery: Addressing barriers to sexual, maternity and reproductive healthcare in Australia’, Canberra: Commonwealth of Australia. Available at

[https://parlinfo.aph.gov.au/parlInfo/download/committees/reportsen/RB000075/toc_pdf/Endingthepostcode lotteryAddressingbarrierstosexual,maternityandreproductivehealthcareinAustralia.pdf](https://parlinfo.aph.gov.au/parlInfo/download/committees/reportsen/RB000075/toc_pdf/Endingthepostcode%20lotteryAddressingbarrierstosexual,maternityandreproductivehealthcareinAustralia.pdf)

² Australian Government Department of Health and Aged Care, (2024), ‘Oral Contraceptives Stakeholder Meeting Outcome Statement’, available at www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/Oral-Contraceptives-Stakeholder-Meeting-October-2024-Outcome-Statement.pdf (accessed 6 February 2025).

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Restriction Summary [new1] / Treatment of Concept: [new1A]
Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Midwives
Restriction type: <input checked="" type="checkbox"/> Restricted benefit
Indication: Contraception
Clinical criteria:
<p>Woman must have at least one of the following:</p> <ul style="list-style-type: none"> • Difficulty swallowing pills; • Gastrointestinal disturbance or malabsorption; • Experienced undesirable side effects with oral contraceptives. <p><i>Patient must have experienced at least one of the following: (i) difficulty swallowing pills (ii) gastrointestinal disorder (iii) gastrointestinal malabsorption (iv) undesirable side effects with oral hormonal contraceptives.</i></p>

- 3.2 The submission indicated that the sponsor was willing to negotiate changes to the wording of the restriction to reduce the risk of use beyond the restriction.
- 3.3 It was unclear whether changes to the restriction wording would mitigate the risk of leakage outside the PBS restriction, especially in the context of a restricted benefit. The risk of use outside the proposed restriction is high.
- 3.4 The letters of support from clinical experts included in the submission did not mention difficulty swallowing pills or malabsorption, but suggested that women who may prefer CVR include:
- those with side effects due to ethinylestradiol (CVR avoids first-pass metabolism);
 - breastfeeding women;
 - women who would prefer not to take medication every day, but equally would prefer not to use a long-acting contraceptive.
- One letter also stated that NuvaRing offered good cycle control.
- 3.5 Only the first of these would confer eligibility under the proposed restriction. Other common circumstances which would not confer eligibility under the proposed restriction but in which CVR may be preferable to COCs have been identified, such as women travelling across multiple time-zones, and women travelling to areas where acute vomiting and diarrhoeal illness is common.³
- 3.6 It was not clear why reasons to prefer CVR other than those listed in the proposed restriction were not included.
- 3.7 Use of oral contraceptives increases the risk of venous thromboembolism (VTE). Combined hormonal contraceptives containing etonogestrel are associated with a

³ Moore P., Streeton C., (2017), ‘Oral hormonal contraception in special circumstances’, Aust Fam Physician, 2017; 46:728-732.

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- greater risk of VTE than those containing levonorgestrel or norethisterone),⁴ and this increased risk appears to apply to CVR as well as to COCs.^{5,6}
- 3.8 The proposed restriction and treatment population was narrower than the TGA approved indication (the TGA approved indication is ‘contraception’, however the proposed restriction is for women who meet the criteria set out in paragraph 3.1).
- 3.9 The PBS listing for the nominated comparator, DMPA, is Unrestricted Benefit, as are current PBS listings for the hormonal contraceptive oral pills and implant. Levonorgestrel intrauterine devices (19.5 mg and 52 mg) are Restricted Benefit listings for ‘Contraception’.
- 3.10 The requested listing provides approximately 12 month’s supply, at the TGA approved dosing. This is consistent with the PBS listings of oral contraceptive medicines. The PBS listing for the nominated comparator, DMPA, provides for up to 6 month’s supply per prescription (1 injection with a maximum of 1 repeat, injection administered every 3 months).
- 3.11 The submission requested that medical practitioners, nurse practitioners and midwives be included as authorised prescribers. This is consistent with the PBS listing for DMPA and the listings for the etonogestrel implant, levonorgestrel intrauterine device and progestogen only pills. Combined oral contraceptives listed on the PBS have medical practitioners and nurse practitioners as authorised prescribers, however at its March 2025 meeting, the PBAC recommended amending all PBS listings for combined oral contraceptives to include endorsed midwives as authorised prescribers.
- 3.12 The Pre-Sub-Committee Response (PSCR) stated that the proposed restriction is deliberately narrow to limit access under the PBS to women who meet the proposed clinical criteria. The PSCR stated that these criteria are based on situations where the bioavailability or tolerability of oral contraceptives are impacted, and claimed that it was unlikely women who did not meet these criteria would be prescribed CVR under the PBS. The PSCR acknowledged the criterion ‘experienced undesirable side effects with oral contraceptives’ can include a broad range of symptoms. The pre-PBAC response maintained that the requested restriction was designed to target a specific population with clinical barriers to the use of oral contraceptives, and claimed the criteria requested are supported by clinical evidence demonstrating reduced bioavailability or tolerability of oral contraceptives in these groups.

For more detail on PBAC’s view, see section 7 PBAC outcome.

⁴ Therapeutic Goods Administration, (2016), ‘Combined hormonal contraceptives’, www.tga.gov.au/news/safety-alerts/combined-hormonal-contraceptives, (accessed 6 March 2025).

⁵ European Medicines Agency, (2014), ‘Combined hormonal contraceptives – referral’, www.ema.europa.eu/en/medicines/human/referrals/combined-hormonal-contraceptives

⁶ RANZCOG, (2024), ‘C-Gyn 3 Contraception’, <https://ranzcof.edu.au/wp-content/uploads/Contraception-Clinical-Guideline.pdf>, (accessed 6 March 2025).

4 Population and disease

- 4.1 The CVR is a plastic (latex free) ring, 54 mm in diameter and 4 mm in cross-section, that is placed in the vagina by the user, left in place for three weeks, and then removed and discarded. The CVR contains ethinylestradiol (EE) and etonogestrel (ENG), a metabolite of desogestrel. The device releases an average of 15 microgram/day of EE and 120 microgram/day of ENG, which are absorbed through the vaginal mucosa. Peak concentrations are reached soon after insertion and then decline, but contraceptive efficacy is maintained for four weeks (though not longer). Compared to users of oral contraceptives with 30 micrograms of EE and 150 micrograms of desogestrel, the peak serum EE concentration is about one third, and the mean concentration is about half, while concentrations of ENG are similar to those of desogestrel.
- 4.2 ENG/EE CVR has the same mechanism of action as COCs and has similar adverse event risks and contraindications.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated DMPA as the primary comparator.
- 5.2 The submission stated:
- “The choice of DMPA as the primary comparator is justified by several key clinical and practical factors:
- **Alternative for women with GI and swallowing issues:** DMPA is often used as an alternative for women who cannot use oral contraceptives due to GI disturbances or malabsorption syndromes, conditions that impact the bioavailability of oral medications. Similarly, NuvaRing's vaginal administration bypasses the gastrointestinal tract, making it suitable for women with these conditions.
 - **Side effect profile:** Women often discontinue oral contraceptives due to side effects such as nausea, vomiting, or breakthrough bleeding. DMPA and NuvaRing, being non-oral, non-surgical alternatives, are commonly used as second-line methods when side effects prevent the use of oral contraceptives. NuvaRing's hormonal profile is associated with lower hormone exposure, leading to better cycle control and fewer side effects, a crucial point for women who have already experienced undesirable effects with oral contraceptives.”
- 5.3 The ESC noted there was a lack of evidence to support the claim that DMPA is often used as an alternative for women who cannot use oral contraceptives due to GI disturbance or malabsorption syndromes.
- 5.4 The ESC noted that guideline recommendations stated that COCs and CVR are equivalent in terms of effectiveness, contraindications/precautions, drug interactions

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- and adverse effects.⁷ The ESC considered the claim that CVR can assist with better cycle control and reduce breakthrough bleeding is supported by clinical guidelines.⁷
- 5.5 The submission also nominated COCs as ‘exploratory’ comparators, including drospirenone with ethinylestradiol (Yaz[®] and Yasmin[®]), recommended for listing by the PBAC at its July 2024 meeting and listed on the PBS in March 2025. The submission stated that drospirenone (Slinda[®]), recommended for listing at the November 2024 PBAC meeting, was not included as an exploratory comparator as no direct clinical data comparing it with the CVR was available. The PSCR reiterated its claim that CVR showed non-inferior safety and efficacy compared to the COCs EE/DRSP and EE/LNG.
- 5.6 The submission presented the results of an online survey of 101 Australian health care providers to understand their prescribing patterns for CVR and DMPA for the proposed PBS population. The questions asked did not address whether DMPA was the treatment most likely to be displaced by the listing of CVR and therefore whether it was appropriate as the primary comparator.
- 5.7 The submission also presented sales data for NuvaRing that identified the type of contraceptive previously used by a cohort of 1,720 patients who used NuvaRing through private scripts. The largest group of NuvaRing users (26.1%) had no prior contraceptive use recorded, suggesting they were not patients unable to tolerate oral contraceptives. The next two largest groups (approximately 6% each) were users of progestogen-releasing IUD and progestogen implant, which were not included as comparators in the submission. Other products listed were a variety of oral contraceptives, but the reasons patients switched from these were not provided – i.e., there is no evidence provided that they would have been eligible under the proposed restriction.
- 5.8 The primary comparator nominated by the submission (DMPA) was not appropriate. The submitted usage data, and the advantages of CVR listed by the clinical experts in input provided in the submission, suggested that CVR will displace not only DMPA but also other hormonal contraceptive options listed on the PBS.
- 5.9 In the context of the cost-minimisation approach taken by the submission, a further consideration for the PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.
- 5.10 For the requested population, allowing for the likelihood of use outside the restriction, all currently listed COCs and progestogen-only pills may be considered alternative therapies because they could be replaced in practice. If use is expected to be effectively limited by the restriction, levonorgestrel IUD and etonogestrel implant may

⁷ Therapeutic Guidelines, 2025. Available at www.tg.org.au (cited Apr 2025).

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be considered alternative therapies. Some of these alternative therapies may be less costly than NuvaRing.

- 5.11 The PSCR and pre-PBAC response maintained that DMPA was an appropriate comparator, especially in the proposed restriction population, as both CVR and DMPA are non-oral, non-daily hormonal contraceptive options. The PSCR and pre-PBAC response claimed both these hormonal contraceptives are used in women who cannot tolerate COCs due to GI disturbances, malabsorption or side effects, and they therefore have a role as alternatives where oral contraceptives are unsuitable.
- 5.12 The PSCR stated that LARCs, such as implants and IUDs, are usually used by women seeking extended-duration, low-maintenance contraception, and require procedural insertion. In contrast, CVR is a monthly self-administered option, and can be used by women seeking a shorter-term, non-oral alternative without invasive intervention.
- 5.13 The PSCR and pre-PBAC response claimed that it would be unlikely the CVR would significantly displace LARC or COC use.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3). The comments stated that CVR is a unique contraceptive and provides another contraceptive option for individuals (including, but not limited to, the groups of women specified in the submission), providing choice. The input stated that ENG/EE CVR may be particularly beneficial for women who face challenges with daily medication routines for various reasons. The input stated that cost is a barrier for many women who might choose this method of contraception, and that listing CVR on the PBS would improve affordability and equity of access.
- 6.3 The National Aboriginal Community Controlled Health Organisation (NACCHO) stated that an advantage of CVR is that it is discretely placed for three weeks, which can benefit people who may not want to be seen taking a tablet daily, or having a visible implant like an etonogestrel rod, however patients require education to ensure correct usage and effective contraception. NACCHO also commented that where medicines are not listed on the PBS, Aboriginal and Torres Strait Islander peoples eligible for the Closing the Gap (CTG) PBS Co-payment program, there is a significant increase in costs to patients, which can risk reduced adherence and subsequent unintended pregnancy. In remote areas where patients access medicines through the Remote Area Aboriginal Health Service S100 Scheme, not having a medicine listed on the PBS can be a barrier to access for these patients.

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- 6.4 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) commented that CVR may result in a lower incidence of breakthrough bleeding, and the lower estrogen dose may reduce estrogen-related side effects, compared to combined oral contraceptives.

Evidence

- 6.5 No evidence was presented to support the efficacy and safety of CVR in the population proposed for PBS-subsidised use. For example, breast tenderness may be less common with CVR than with COCs, but it does occur,⁸ and no evidence was presented to show that women with troublesome breast tenderness with COCs do not have troublesome breast tenderness with CVR. No evidence was presented that women who had difficulties with adherence to COCs had less frequent or less severe difficulties with adherence to CVR. This was acknowledged by the submission.
- 6.6 As well as the formal claims of non-inferiority in contraceptive efficacy and safety, the submission made a number of claims of superiority of CVR to COCs or DMPA. These were not well-supported by evidence.
- 6.7 The submission stated that the CVR has been associated with higher levels of patient satisfaction and tolerability, citing Zapata (2024)⁹ which stated that "90% of NuvaRing users reported being "very satisfied" with the method at 6 months, compared to 73.7% of DMPA users". This was not correct: Zapata (2024) reports continuing use and satisfaction data for CVR and contraceptive patch together (numbers were relatively small) and only 46.4% of women started on CVR or patch were still using that method after 6 months, of whom 93.8% were "very satisfied". Furthermore, the participants in the study were not limited to the population requested in the proposed PBS restriction.
- 6.8 The submission stated that Indigenous women were more likely to use DMPA, because of limited access to alternatives, and that Indigenous women were reluctant to use a LARC because of their experiences of coercive or non-consensual implanted or permanent contraception. The cited reference (Griffiths (2016))¹⁰ studied Indigenous women in three remote Western Australian communities. They reported that 191/566 (33.7%) women had used high-efficacy contraception during the study period (1 November 2010 – 1 September 2014) and 113 (20%) were using it at the date of survey; 93/113 (82.3%) were using etonogestrel implant and 9/113 (8%) were using

⁸ Lopez (2013) estimated a pooled odds ratio (95% CI) for breast tenderness with CVR vs COC containing drospirenone 3 mg and ethinylestradiol 30 mcg of 0.81 (0.47, 1.4) based on two trials with total N = 1,467.

Lopez L.M., Grimes D.A., Gallo M.F., et al, (2013), 'Skin patch and vaginal ring versus combined oral contraceptives for contraception', *Cochrane Database Syst Rev*, 2013(4):CD003552.

⁹ Zapata L.B., Kortsmid K., Curtis K.M., et al, (2024), 'Continuation of reversible contraception following enrollment in the Zika Contraception Access Network (Z-CAN) in Puerto Rico, 2016–2020', *Stud Fam Plann*, 55(2):105–25. Available at: <https://doi.org/10.1111/sifp.12262>.

¹⁰ Griffiths E.K., Marley J.V., Friello D., et al, (2016), 'Uptake of long-acting, reversible contraception in three remote Aboriginal communities: a population-based study', *Med J Aust*, 205(1):21–5.

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DMPA; no woman was using a COC. Satisfaction with the etonogestrel implant was high, with most women providing positive feedback with its use. One individual 'reported suspicions in the community that it had secondary purposes: "it controls them"'.¹⁰ The cited evidence does not support a view that Indigenous women are reluctant to use a LARC, that they use DMPA because they have no alternative if they cannot use COCs, or that they would switch to CVR if it was PBS-listed.

- 6.9 The PSCR maintained that Griffiths (2016) supported the claim that there would be potential interest in the CVR by Indigenous women. The PSCR provided an additional reference (Harris (2021))¹¹ and stated that this study found that women living in remote areas were significantly more likely to use DMPA compared to women living in major cities (OR = 3.90, 95% CI: 1.84–6.19), and women with a history of intimate partner violence were around 50% more likely to use DMPA compared to women without this history (OR = 1.57, 95% CI: 1.19–2.03). It concluded that these findings demonstrated constrained access to alternative methods (e.g. COCs, LARCs) rather than true preference. The PSCR claimed that these findings show a need for a wider range of non-oral, user controlled and reversible contraceptive methods, and that CVR is well positioned to address this gap, especially for women who are unable or unwilling to use COCs or LARCs.
- 6.10 The Harris (2021) study was an Australian cohort study and did not report data for Indigenous women. The odds ratios cited in the PSCR for women living in remote areas and with a history of intimate partner violence were for the rate of using sterilisation methods, not the rate of using DMPA. The odds ratio for using sterilisation methods in women with intimate partner violence was compared to the rate of using short-acting contraceptives (which included DMPA) and condoms.
- 6.11 A key claim of the submission was that "women with GI (gastrointestinal) conditions (such as malabsorption syndromes, inflammatory bowel disease, or post-bariatric surgery) face further challenges with OC efficacy, as these conditions impair the absorption of hormones from OCs, leading to reduced contraceptive effectiveness".
- 6.12 Although it is well known that vomiting and diarrhoea, whatever the cause, can reduce the effectiveness of COCs, the submission presented no evidence of reduced oral contraceptive effectiveness in these patient groups. A non-systematic search during the evaluation did not find any reports of reduced effectiveness of COCs in trials or cohort studies enrolling patients with these conditions, and some that found the contrary.^{12,13}

¹¹ Harris M.L., Egan N., Forder P.M., et al, (2021), 'Contraceptive use among women through their later reproductive years: Findings from an Australian prospective cohort study', PLoS One 16(8):e0255913.

¹² Daoud N.D., Ghoz H., Cannon R., et al, (2022), 'Oral contraceptive pills are an effective method of preventing pregnancy in women with Crohn's Disease', Crohn's and Colitis 360, 4:1-4.

¹³ Whiteman M.K., Oduyebo T., Zapata L.B., Walker S., Curtis K.M., (2016), 'Contraceptive safety among women with cystic fibrosis: A systematic review', Contraception, 94:621-9.

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- 6.13 COCs are not generally contraindicated in women with gastrointestinal disorders. Guidelines of the US Centers for Disease Control,¹⁴ World Health Organization,¹⁵ and UK Faculty of Sexual and Reproductive Health (FSRH)¹⁶ (on which the RANZCOG guidelines are based) all treat CVR and COCs as interchangeable – i.e., problems with malabsorption and efficacy are not common or not supported by evidence. None of these guidelines mentions dysphagia or coeliac disease. The UK Faculty of Sexual and Reproductive Health guidelines states that the absorption of COCs in women with ‘mild ulcerative colitis and no or small ileal resections is similar to the absorption among healthy women. Findings may not apply to women with Crohn’s disease or more extensive bowel resections.’¹⁶ In inflammatory bowel disease, the concern is thromboembolic risk, and for both COCs and CVR the advantages of using the method generally outweigh the risks except when the risk of venous thromboembolism is increased, for example, in patients having surgery or are immobilised.
- 6.14 With regard to bariatric surgery, there is no concern with the use of COCs in patients who have had restrictive procedures, including sleeve gastrectomy (stated in the submission to be the most common procedure in Australia) and COC use is relatively contraindicated only in patients who have had diversionary procedures. For patients with a history of bariatric surgery malabsorptive procedures, there are no restrictions for the use of the CVR, however for COCs the risks can outweigh the advantages of use (the procedure has potential to reduce contraceptive effectiveness, and this may be further decreased by post-operative complications such as diarrhoea or vomiting).¹³
- 6.15 The PSCR stated that the FSRH guidelines recommend that women who have had bariatric surgery should be advised of potential reduced effectiveness of COCs and should consider a non-oral method of contraception. With regards to bariatric surgery and combined hormonal contraception, the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) state that there is limited evidence which shows there is no substantial reduction in the effectiveness of oral contraception in women who have laparoscopic placement of an adjustable gastric band or biliopancreatic diversion. However, there are conflicting results from the evidence of the effectiveness of oral contraception in patients who have had jejunioileal bypass.¹⁵
- 6.16 The submission stated that rapid and reliable early return of fertility (within 3-4 weeks) was an advantage of CVR, especially compared to DMPA. The submission cited the statement in the Product Information (PI) for Depo-Provera® that with DMPA "return

¹⁴ U.S. Centers for Disease Control and Prevention, (2024), ‘U.S. medical eligibility criteria for contraceptive use, 2024’, Centers for Disease Control and Prevention: Atlanta, GA. Available at www.cdc.gov/mmwr/volumes/73/rr/pdfs/rr7304a1-H.pdf accessed 7 January 2025.

¹⁵ World Health Organization, (2015), ‘Medical eligibility criteria for contraceptive use’, World Health Organization: Geneva. Available at https://iris.who.int/bitstream/handle/10665/181468/9789241549158_eng.pdf?sequence=9 accessed 7 January 2025.

¹⁶ The Faculty of Sexual & Reproductive Healthcare, (2019), ‘UK medical eligibility criteria’, Faculty of Sexual and Reproductive Healthcare: UK. Available at www.fsrh.org/Common/Uploaded%20files/documents/fsrh-ukmec-full-book-2019.pdf accessed 7 January 2025.

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to fertility can take up to 18 months following the last injection". Persistent amenorrhoea after stopping DMPA is a recognised adverse event, but the frequency is low: the PI also states that of women stopping Depo-Provera in order to become pregnant, 93% will have conceived within 18 months (p7). Using the generally accepted figure of 80-90% for the proportion of women at risk of pregnancy who will conceive within one year,¹⁷ the proportion expected not to have conceived within 18 months is 2-7%.

- 6.17 A recent systematic review found that the rate of pregnancy within 12 months of stopping contraception did not differ with different methods of contraception (contraceptive methods included in the review were implants, injections, intrauterine devices and oral contraceptives).¹⁸ The PSCR argued that this systematic review did not include DMPA, and therefore its findings were not relevant to this submission.

Clinical trials

- 6.18 The submission identified no head-to-head trials comparing CVR with DMPA. The submission relied on two indirect treatment comparisons of CVR and DMPA, with COC (EE 30 micrograms + levonorgestrel 150 micrograms) and norethisterone enanthate (NET-EN) 200 mg intramuscular injection as common comparators.
- 6.19 A number of head-to-head trials of CVR vs COCs were identified by the submission's literature search that could have been included in the indirect treatment comparison but were not (10 excluded trials were shaded grey in Table 2.2.1). Two trials (Fan (2016) and Ahrendt (2006)) were large one-year trials comparing CVR with COC and should be included. It is stated that the reasons for exclusion were included in Attachment 5a, but in that attachment all of the trials are marked "Include". It is not clear why these trials were excluded; Fan (2016) and Ahrendt (2006) did not use the COC EE 30 micrograms + levonorgestrel 150 micrograms as the comparator (as the included trials Duijkers (2004), Gill (2020) and Oddsson (2005a, 2005b) did), however the included study of Hubacher (2018) also did not use exclusively the COC EE 30 micrograms + levonorgestrel 150 micrograms. The PSCR stated that these trials were included in Attachment 12a of the submission. However these trials are not included in Table 2.2.2 'Trials (and associated reports) presented in the submission'.
- 6.20 The data sources for all studies are published papers. Because of the age of the publications, significant amounts of information, such as the planned statistical analyses, inclusion and exclusion criteria (or whether there were formal criteria) and baseline characteristics are missing in many cases.

¹⁷ Food and Drug Administration, (2019), 'Establishing effectiveness and safety for hormonal drug products intended to prevent pregnancy. Guidance for industry', U.S. Department of Health and Human Services. Available at www.fda.gov/media/128792/download accessed 9 January 2025.

¹⁸ Girum T., Wasie A., (2018), 'Return of fertility after discontinuation of contraception: a systematic review and meta-analysis', *Contraception & Reproductive Medicine*, 23:3:9.

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- 6.21 Details of the trials presented in the submission are provided in Table 2. The study of Hubacher is included under the heading of trials with a common arm of EE 30 micrograms + levonorgestrel 150 micrograms because it is included under that heading in Table 2.3.1 of the submission, but several different COCs were used in the trial and it is not stated that all or any were EE 30 micrograms + levonorgestrel 150 micrograms.
- 6.22 . The study of Hubacher is included under the heading of trials with a common arm of EE 30 micrograms + levonorgestrel 150 micrograms because it is included under that heading in Table 2.3.1 of the submission, but several different COCs were used in the trial and it is not stated that all or any were EE 30 micrograms + levonorgestrel 150 micrograms.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
ITC of CVR vs DMPA with COC as common comparator		
CVR vs EE30/Lev150		
Duijkers, 2004	A comparative study on the effects of a contraceptive vaginal ring NuvaRing® and an oral contraceptive on carbohydrate metabolism and adrenal and thyroid function.	European Journal of Contraception and Reproductive Health Care, 2004; 9:131-140.
Gill, 2020 NCT02404038	An open-label, randomized crossover study to evaluate the acceptability and preference for contraceptive options in female adolescents, 15 to 19 years of age in Cape Town, as a proxy for HIV prevention methods (UChoose)	Journal of the International AIDS Society, 2020; 23:e25625.
Oddsson, 2005a Oddsson, 2005b	Superior cycle control with a contraceptive vaginal ring compared with an oral contraceptive containing 30 microg ethinylestradiol and 150 microg levonorgestrel: a randomized trial.	Human Reproduction, 2005; 20:557-562.
	Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial.	Contraception, 2005; 71:176-182.
DMPA vs EE30/Lev150		
Hubacher, 2017 ¹ Hubacher, 2018 ¹	Long-acting reversible contraceptive acceptability and unintended pregnancy among women presenting for short-acting methods: a randomized patient preference trial.	Am J Obstet Gynecol 2017; 216:101-109.
	Not seeking yet trying long-acting reversible contraception: A 24-month randomized trial on continuation, unintended pregnancy and satisfaction.	Contraception, 2018; 97:524-532.
ITC of CVR vs DMPA with NET-EN as common comparator		
CVR vs NET-EN		
Gill, 2020 NCT02404038	An open-label, randomized crossover study to evaluate the acceptability and preference for contraceptive options in female adolescents, 15 to 19 years of age in Cape Town, as a proxy for HIV prevention methods (UChoose).	Journal of the International AIDS Society, 2020; 23:e25625.
DMPA vs NET-EN		
Benagiano, 1977 Benagiano, 1978	Multinational comparative clinical evaluation of two long-acting injectable contraceptive steroids: norethisterone oenanthate and medroxyprogesterone acetate. 1. Use-effectiveness.	Contraception, 1977; 15:513–533.
	Multinational comparative clinical evaluation of two long-acting injectable contraceptive steroids: Norethisterone oenanthate and medroxyprogesterone acetate: 2. Bleeding patterns and side effects ¹	Contraception, 1978; 17:395–406.
Salem, 1988	Acceptability of injectable contraceptives in Assiut, Egypt.	Contraception, 1988; 38:697–710.
Singata-Madliki, 2024	Effects of injectable contraception with depot medroxyprogesterone acetate or norethisterone enanthate on estradiol levels and menstrual, psychological and behavioural measures relevant to HIV risk: The WHICH randomized trial.	PloS One, 2024; 19:e0295764.
Swenson, 1980	A randomized, single blind comparative trial of norethindrone enanthate and depo-medroxyprogesterone acetate in Bangladesh.	Contraception, 1980; 21:207–215.

Source: Table 2.2.2, pp55-56 of the submission main body.

¹ Hubacher, 2018, presents data from 24 months of follow-up and Hubacher, 2017, data for the first 12 months with some additional information. The trial did not use only COC with EE30+Lev150 and may not have used any.

COC = combined oral contraceptive; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; EE30 = ethinylestradiol 30 micrograms; ITC = indirect treatment comparison; Lev150 = levonorgestrel 150 micrograms; NET-EN = norethisterone enanthate. Norethisterone is known as norethindrone in the USA.

6.23 The key features of the trials are summarised in

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6.24 Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias*	Patient population	Outcome(s)
Duijkers, 2004	85, but data presented only for 77 (8 women withdrew after randomisation but before starting study medication)	OL, MC, R but method not adequately described and in blocks of 4; CVR vs COC, duration six cycles of 28 days; withdrawals not adequately accounted for and adverse events not properly reported.	High	Healthy women aged 18-40, seeking contraception; BMI 18-29 kg/m ² , allocated to CVR or COC.	Glucose, insulin, glycosylated Hb, total cortisol, CBG, DHEA; TSH, free thyroxine.
Gill, 2020 NCT02404038	130	OL, R (method not stated) 1:1:1 CVR/NET-EN/COC for first 16 weeks, then all on NET-EN or COC switched to CVR, and those on CVR switched to their choice of NET-EN or COC for further 16 weeks. Switching between methods allowed and required for poor compliance but duration of exposure to each method not reported, but self-reported adherence with each method was reported.	High	Healthy, sexually active HIV-negative women aged 15-19 years; low-income area of Cape Town with high HIV risk; recruitment via community outreach at local school, clinic and youth groups.	Primary outcomes: Acceptability and preference of contraceptive method, as a surrogate for acceptability of HIV-prevention by vaginal ring, injection or daily pill.
Oddsson, 2005a, 2005b	1,030; 1,079 randomised but 49 withdrew (29 CVR, 20 COC) and not included in ITT	OL, R, MC, 1 year (13 cycles); CVR = 512, COC = 518	Unclear	Healthy women aged 18 or over, seeking contraception.	Primary outcomes: Cycle control/vaginal bleeding characteristics (reported in Oddsson, 2005a).
Hubacher, 2017, 2018 NCT01299116	916	OL, partially R (method not stated); patients preferring COC or DMPA used (and paid for) that method (N = 524); patients agreeing to be R (N = 392) provided (free) either LARC (patients chose subdermal implant, Cu-IUD or hormonal IUD) or SARC (patients chose COC or DMPA). Patients could switch freely among methods, but pregnancies were tallied to the method first used.	High	Healthy women aged 18-29 years, seeking COC or DMPA, sexually active, no previous use of an IUD or subdermal implant, not pregnant or seeking a pregnancy termination on day of screening.	Contraceptive discontinuation; restarts or switches; unintended pregnancy at 12 months.

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Trial	N	Design/duration	Risk of bias*	Patient population	Outcome(s)
Benagiano, 1977, 1978	1,678	OL, MC, R (inadequate method), DMPA vs NET-EN; 2 years but stopped after 1 year because pregnancy rate with NET-EN exceeded the pre-specified stopping rule of a maximum of 2 pregnancies per 100 women years.	High	Healthy women with previous live birth in the past 5 years, aged 18-40 years.	Pregnancy, treatment discontinuation, (medical and non-medical reasons separated).
Salem, 1988	400	OL, R (inadequate method) DMPA vs NET-EN; 1 year.	High	Healthy women of "proven fertility" aged 18-40.	Menstrual pattern, treatment discontinuations.
Singata-Madliki, 2024	521 (453 completed the study)	OL, R, DMPA vs NET-EN, 25 weeks.	Unclear	Women aged 18-40 years, requesting injectable contraception, intending to use contraception for ≥ 18 months and declining pre-exposure prophylaxis for HIV.	Primary outcome: 17 β estradiol levels, depression score.
Swenson, 1980	239	OL, R (method not stated); randomised 1:1 DMPA vs NET-EN but 133 received DMPA and 106 NET-EN, because for a time supplies of NET-EN ran out and for that period all women were given DMPA; 1 year but 47% completed 6 months and 12% one year.	High	Women agreeing to receive an injectable contraceptive with at least one living child.	Menstrual pattern, treatment discontinuations, pregnancy rates.

Source: Constructed during the evaluation from the published reports.

BMI = body mass index; CBG = cortisol binding globulin; COC = combined oral contraceptive; Cu = copper; CVR = contraceptive vaginal ring; DHEA = dehydroepiandrosterone; DMPA = depot medroxyprogesterone acetate; Hb = haemoglobin; HIV = human immunodeficiency virus; ITT = intention to treat; IUD = intrauterine device; LARC = long-acting reversible contraceptive; MC = multi-centre; NET-EN = norethisterone enanthate; OL = open label; R = randomised; SARC = short-acting reversible contraceptive; TSH = thyroid stimulating hormone.

*Added during evaluation

6.25 There were major methodological issues with most of these studies (see

6.26 **Table 3**).

6.27 As well as all trials being open label, the methods of randomisation were either not stated or inadequate in all except Oddsson (2005a, 2005b) and Singata-Madliki (2024).

6.28 Hubacher (2017, 2018) was not a randomised comparison of COC and DMPA.

6.29 The purpose of the Hubacher study was to test the hypothesis that many women who do not intend to use long-acting reversible contraception (LARC) might find it acceptable or preferable if they could be persuaded to try it. Women who presented for contraception and stated either that they wished to use COCs or that they wished to use DMPA were recruited; those who had previously used LARC were excluded. Patients could enter the trial but use the method they had sought – COCs or DMPA –

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in which case they paid for it as normal; 524/916 (57.2%) patients chose this option. If patients agreed to be randomised, the randomised treatment was provided free of charge for one year; 392/916 (42.8%) patients agreed to be randomised, of whom 60% did so because the treatment was free. Randomisation was to SARC vs LARC; patients randomised to SARC chose between COCs and DMPA, and those randomised to LARC chose between subdermal implant, levonorgestrel IUD, or copper IUD. Of 524 patients choosing not to be randomised 423/524 (80.7%) used COCs and 99/524 (18.9%) used DMPA; of 198 patients randomised to SARC, 147/198 (74.2%) chose COC and 48/198 (24.2%) chose DMPA.¹⁹

- 6.30 Patients were free to switch between contraceptive modalities or to stop using any method while remaining in the trial, but pregnancies were counted against the method they started on, not the method (if any) they were using when they conceived. This was reasonable, given the aim of the study, but it means that the reported pregnancy rate may be an over-estimate if patients discontinuing a method stopped using any contraception, or an under-estimate if the patients switched to a more effective method. This would especially affect methods with a high rate of discontinuation, i.e., DMPA.
- 6.31 That this may have influenced the results is suggested by a study intended to promote LARC use in a similar population to that of Hubacher (2017, 2018), in which 7,486 women were provided with their choice of contraception at no cost. Patients could switch methods of contraception freely, but those who conceived were asked which, if any, method they were using at the time, and the pregnancy was tallied against that method. In this cohort, there were 156 unintended pregnancies, 21 in women using LARC (0.27/100 woman years), 2 in women using DMPA (0.22/100 woman years) and 133 in women using pills/patches/CVR (4.55/100 woman years).²⁰
- 6.32 Loss to follow-up was high in several studies, which makes data for pregnancies problematic when very few pregnancies were recorded. In Gill (2020), 22/130 (16.9%) patients were lost to follow-up in the first 16 week period and 15/108 (13.9%) in the second 16 weeks. In Salem (1980), 65/400 (16.2%) were lost to follow up. In Swenson (1980), only 28/239 (11.7%) were still in the study at one year.
- 6.33 The trial reported by Benagiano (1977, 1978) is particularly important because of its size, which means that it dominates the meta-analysis of DMPA versus NET-EN. This trial was stopped early because the number of pregnancies in the NET-EN group met the pre-specified stopping rule (3.6 (SE 0.7) pregnancies per 100 woman years in the NET-EN group vs 0.7 (SE 0.7) in the DMPA group). However, two of 10 centres

¹⁹ These data were provided in Table 2.5.2, p82 of the submission main body. The source is unclear, because the submission stated that the source was Table 2 of Hubacher (2017) and Table 3 of Hubacher (2018), but those tables do not contain the data.

²⁰ Winner B., Peipert J.F., Zhao, Q., et al, (2012), 'Effectiveness of long-acting reversible contraception', *N Engl J Med* 2012; 366:1998-2007.

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(Bangkok and Chandigarh) contributed 13/24 (54%) pregnancies in the NET-EN group but only 19% of woman years of exposure. There was also very marked variation among centres in the rate of treatment discontinuation for medical reasons: in Chandigarh over 50% of patients allocated to NET-EN and 80% allocated to DMPA had discontinued at 24 weeks, while in Bombay less than 10% of women allocated to either treatment had discontinued at 24 weeks. Such large differences in outcome by centre cast doubt on the generalisability of the results.

- 6.34 In the trial of Swenson (1980), women who wished to discontinue because of amenorrhoea "were not given estrogens to induce withdrawal bleeding in order to encourage them to continue with the injectables". As well as being unethical, this makes it difficult to interpret discontinuations, given that amenorrhoea was commoner among women receiving DMPA and was the commonest identified reason for discontinuation. The number of pregnancies in this study is unclear; 13 women reported being pregnant, of whom two "had menstrual irregularities with uncertain reports" (?) and two were lost to follow-up after reporting their pregnancy. Pregnancy was confirmed at the clinic in nine, but 11 pregnancies are reported in the data.
- 6.35 There were also transitivity issues with the included studies. It is well known that many methods of contraception are much less effective in typical use than when used perfectly. For example, Family Planning NSW (2024) gives values for contraceptive efficacy in perfect/typical use of 99.8/96% for injections, 99.5/93% for CVR, and 99.5/93% for COCs (Figure 1.1.1 of the submission). The only comparison of COCs with DMPA (Hubacher), and two of the studies of DMPA with NET-EN (Salem and Swenson) were in typical-use situations, but only data from controlled trials was used for CVR. The ITC requires the assumption that the difference between efficacy in perfect and typical use for CVR is identical to the difference between perfect and typical use for COCs and DMPA, for which there does not appear to be evidentiary support.
- 6.36 Gill (2020), is key to the indirect treatment comparison with NET-EN as common comparator. The purpose of this trial was to assess the likely acceptability of the vaginal rings, depot injections, and daily pills as means of delivering pre-exposure HIV prophylaxis (PrEP) to young women at high risk of HIV infection. The women in this study were not seeking contraception – most (97/130, 74.6%) were current users of contraception, nearly all NET-EN or DMPA (88/97, 90.7%). CVR, NET-EN injections and COCs were chosen only because they were already available products that provide a similar user experience to the proposed PrEP products.
- 6.37 In Gill (2020), because the focus of the study was not contraception, women who were not using CVR correctly were switched to another method by study staff early in the study in order to avoid pregnancy (Gill (2020), p8). Women were also free to switch from one method to another that they preferred. Overall, 8/45 (17.7%) women switched from CVR during the first 16 week period and 16/71 (22.5%) did so in the second 16 week period. At what point during the treatment period patients switched was not reported, so the duration of use of each contraceptive method cannot be

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determined (Table 2.4.14 of the submission). This was reasonable, given the aim of the study, but does not provide data to calculate a rate of pregnancy.

- 6.38 The PSCR acknowledged that there was limited trial data available specifically for the population in the proposed restriction, and claimed that to address this all randomised quality trials comparing CVR and DMPA were included, to allow evaluation of safety and efficacy. The PSCR claimed that this would inform the outcomes in the PBS-intended population. The PSCR claimed that undertaking sensitivity analyses and meta-analyses increased the reliability of the results.
- 6.39 The pre-PBAC response also acknowledged the limited trial data for women with gastrointestinal issues or swallowing difficulties, but cited van den Heuvel (2005) to support its claim that CVR has fewer estrogen-related side effects compared to COCs. The pre-PBAC response stated that to address the limited trial data, the submission included all relevant randomised controlled trials comparing CVR and DMPA. Eight randomised controlled trials were synthesised via meta-analyses, with sensitivity analyses to ensure reliability despite study heterogeneity.
- 6.40 The PSCR acknowledged that the studies of DMPA were older, however maintained that they were the most relevant and available data, and that findings demonstrated that CVR and DMPA have similar contraceptive efficacy.

Comparative effectiveness

- 6.41 The number and rates (where calculable) of unintended pregnancy in the studies used in the indirect treatment comparison for CVR vs DMPA with COC as the common comparator are shown in Table 4.

Table 4: Unintended pregnancies in the submitted trials for ITC of CVR vs DMPA via COC

	CVR	COC	Relative Risk (95% CI)	Risk Difference (95% CI)
Duijkers, 2004				
Pregnancy n/N, (%)	0/44 (0%)	0/41 (0%)	NE	0.0% (-4.5, 4.5)
Gill, 2020				
Pregnancy n/N (%)	1/116 (0.9%)	0/48 (0%)	1.3 (0.05, 30.3)	0.9% (-2.6, 4.3)
Oddsson, 2005				
Pregnancy n/N (%)	5/512 (1.0%)	5/518 (1.0%)	1.01 (0.29, 3.47)	0.01% (-1.2, 1.2)
Meta-analysis of 3 trials	6/672 (0.9%)	5/607 (0.8%)	1.04 (0.33, 3.29)	0.10% (-1.0, 1.2)
	DMPA	COC		
Hubacher (2017, 2018)				
Pregnancy n/N ¹	NR	NR		
% at 1 year	4.6	6.1	0.78 (0.35, 1.71)	-1.4% (-5.4, 2.6)
% at 2 years	11.5	8.5	1.37 (0.81, 2.32)	3.1% (-2.5, 8.8)

Source: Tables 2.5.1, p81, 2.5.2, p82, 2.6.2, p89, 2.6.3, p90 of the submission.

¹ A total of 34 unintended pregnancies were reported at 1 year and 60 at 2 years in women using COCs or DMPA.

CI = confidence interval; COC = combined oral contraceptive; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; ITC = indirect treatment comparison; NE = not evaluable; NR = not reported.

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6.42 The number and rates (where calculable) of unintended pregnancy in the studies used in the indirect treatment comparison for CVR vs DMPA with NET-EN as the common comparator are shown in Table 5.

Table 5: Unintended pregnancies in the submitted trials for ITC of CVR vs DMPA via NET-EN

	CVR	NET-EN	Relative Risk (95% CI)	Risk Difference (95% CI)
Gill, 2020				
Pregnancy, n/N (%)	1/116 (0.9%)	0/73 (0%)	1.9 (0.1, 46.0)	0.9% (-1.9, 3.6)
	DMPA	NET-EN		
Benagiano, 1977, 1978				
Pregnancy, n/N (%)	6/846 (0.7%)	24/832 (2.9%)	0.25 (0.10, 0.60)	-2.2% (-3.4, -0.9)
Salem, 1988				
Pregnancy, n/N (%)	1/200 (0.5%)	2/200 (1%)	0.50 (0.04, 5.5)	-0.05% (-2.2, 1.2)
Swenson, 1980				
Pregnancy, n/N (%)	5/133 (3.8%)	6/106 (5.7%)	2.0 (0.2, 22.2)	-1.9% (-7.4, 3.6)
Singata-Madliki, 2024				
Pregnancy, n/N (%)	2/223 (0.9%)	1/226 (0.4%)	2.0 (0.2, 22.2)	0.45% (-1.1, 2.0)
Meta-analysis of 4 trials	14/1,402 (1.0%)	33/1,364 (2.4%)	0.45 (0.21, 0.98)	-0.09 (-2.5, 0.7)

Source: Tables 2.5.3, p82, 2.5.4, p83, 2.6.9, p94, 2.6.10, p95 of the submission.

CI = confidence interval; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; ITC = indirect treatment comparison; NET-EN = norethisterone enanthate.

6.43 For both CVR vs COC and DMPA vs NET-EN results from the meta-analyses are limited, because both are dominated by a single trial. As noted above (paragraph 6.33) this is especially problematic in the case of Benagiano (1977, 1978), because of generalisability concerns.

6.44 The pre-PBAC response stated that the submission provided comprehensive clinical evaluations of CVR against COCs, including four randomised controlled trials for CVR versus EE/DRSP (Ahrendt (2006), Battaglia (2014), Fan (2016), Mohamed (2011)) and three randomised controlled trials for CVR versus levonorgestrel/ethinylestradiol. These were not included in the ITC (see paragraph 6.19).

6.45 The pre-PBAC response stated that key findings from these evaluations included:

- CVR had non-inferior efficacy compared to EE/DRSP (no significant difference in unintended pregnancies), with potential benefits in cycle control and sexual satisfaction. Tolerability was comparable, with CVR showing fewer estrogen-related adverse events (e.g., nausea).
- CVR had similar efficacy to levonorgestrel with ethinylestradiol with similar adherence, discontinuation rates, and adverse events. Lower estrogen exposure with CVR (van den Heuvel et al., 2005) reduced side effects like breast tenderness and bloating, enhancing tolerability.

Indirect treatment comparison

6.46 Both indirect treatment comparisons (ITCs) are compromised by trial quality and by transitivity issues. The ITC of CVR vs DMPA via COC depends on the study of Hubacher (2017, 2018), which was not a randomised trial of COC vs DMPA and should not have been used.

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6.47 The results of the indirect treatment comparisons for unintended pregnancy are shown in Table 6.

Table 6: Indirect treatment comparisons for unintended pregnancy of CVR vs DMPA with common comparators of COC and NET-EN

	Relative Risk (95% CI)	Risk Difference (95% CI)
CVR vs DMPA via COC RR less than 1 or negative RD favours CVR	0.79 (0.22, 2.87)	-3.1% (-8.8, 2.7)
CVR vs DMPA via NET-EN RR less than 1 or negative RD favours CVR	NE	2.3% (0.3, 4.2)

Source: Table 2.6.20, p109 of the submission main body. Results in **bold** are statistically significant.

CI = confidence interval; COC = combined oral contraceptive; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; NE = not evaluable; NET-EN = norethisterone enanthate; RD = risk difference; RR = relative risk.

6.48 The comparison via COC non-significantly favours CVR in terms of contraceptive efficacy and the comparison via NET-EN significantly favours DMPA. Differences in pregnancy risk of 5% (-3% to +2%) would be clinically significant, and this degree of inconsistency between comparisons with different common comparators casts doubt on the reliability of the results.

6.49 The submission also presented meta-analyses and indirect treatment comparisons for adherence and for the number of patients discontinuing use, although these outcomes were not part of the clinical claim.

6.50 Data for adherence were presented only from Gill (2020) and Oddsson (2005a, 2005b).

6.51 Gill (2020) reported only the proportion of patients who said their use was "exactly as instructed", but this phrase was not defined in the published report. Further, patients not using CVR correctly were switched to another method by study staff early in the study in order to avoid pregnancy (Gill (2020), p8), so the reported rates of correct use of CVR were likely inflated by removing these women from the CVR sample before any data was collected.

6.52 The value from Gill (2020) given in the submission for "complete adherence" (135/173, 78%) was misleading. Patients filled out adherence questionnaires every 8 weeks (i.e., twice in each treatment period), and 78% was the proportion of questionnaires in which use exactly as instructed in the past 2 months was reported. Complete adherence should be the number of participants who reported use exactly as instructed in both questionnaires in a 16 week treatment period, but this was not reported. A majority of the data was missing: there should have been 216 completed questionnaires for the first 16 week period and 188 for the second 16 weeks (total 404). There was a high lost to follow-up rate.

6.53 Data for discontinuations was also problematic for methodological reasons. This was particularly the case for studies of DMPA, with failure to distinguish study discontinuation from treatment discontinuation in Salem (1988) and Swenson (1980), which makes the data very difficult to interpret, and generalisability concerns in

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Benagiano (1977, 1978) arising from marked differences in discontinuations among study centres.

- 6.54 In Hubacher (2017, 2018), there were no scheduled follow-up visits for study purposes; patients attended only for clinical reasons. Data (including reason for the visit, any contraceptive method provided or switching of contraception) was collected at these visits and by on-line questionnaires at 6, 12, 18 and 24 months (including the main reason for any switch or discontinuation of any contraceptive method and pregnancy plans). Data sources for DMPA users who needed to attend the clinic regularly were therefore different from data sources for users of COCs or LARC. The definitions of discontinuation also differed by method: for DMPA it was a clinic record of non-attendance for a repeat injection, and for LARC it was a clinic record of removal, while for COCs it was patient report. Because the data sources were different, the data are subject to different biases and sources of error and are difficult to compare.
- 6.55 For these reasons, the adherence and discontinuation data will not be presented in the evaluation.

Comparative harms

- 6.56 Adverse event reporting in a number of the trials was problematic.
- 6.57 The older trials (Benagiano (1977, 1978), Swenson (1980) and Salem (1988)) did not follow current standards of reporting. Benagiano (1978), states that "[a]t each follow-up visit a variety of symptoms were volunteered, but many events were either too nonspecific or too infrequent to permit detailed analysis" and reports only the proportion of women who "[o]ver the duration of the study [...] registered some complaint".
- 6.58 Due to studies of DMPA vs NET-EN not reporting adverse effects consistently, the submission used data from Benagiano (1977, 1978), Salem (1988) and Swenson (1980) for discontinuation for "medical reasons" as a proxy for adverse events (Table 2.5.8 of the submission); this was not appropriate.
- 6.59 Hubacher (2017, 2018) and Singata-Madliki (2024) did not report adverse events.
- 6.60 Duijkers (2004) reported that six subjects allocated to CVR withdrew, one due to adverse event (vaginal discomfort), and five for "non-medical or ring related reasons". Two subjects allocated to COCs withdrew, one due to adverse event (increased appetite) and one for "non-medical reasons". What the non-medical reasons were is not stated.
- 6.61 In Gill (2020) adverse event reporting did not follow standard procedures. It was stated that "[t]here were no serious adverse events (AEs) noted on this trial", but there was one new HIV infection and 16 new infections with *N. gonorrhoeae* during the trial (Gill, 2020, p4, Table 2). It was stated that "[o]nly 15% of reported AEs were related to study product use and included already recognized side effects of hormonal contraceptives, such as abnormal uterine bleeding, headaches, mastalgia and weight

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gain", but patients using CVR reported among reasons for not using it as instructed "Ring came out", "Ring was uncomfortable", and "Did not like the way ring made them feel". It is not clear whether these were considered adverse events. This approach to adverse events was defensible given the purpose of the trial but makes it unsuitable as a source of adverse event data for the purpose of the submission.

- 6.62 For Gill (2020), the submission used as adverse event data the number of participants who preferred the CVR but did not give as their reason for preferring it "Did not make me sick" (Table 2.5.6 of the submission); this was not appropriate.
- 6.63 Adverse event data for trials from which adverse event data could be extracted are presented in Table 7.
- 6.64 Some systemic adverse events (e.g., hypertension, acne) were more common with COCs, and local adverse events (e.g., vaginitis leukorrhoea, genital itch) were more common with CVR.

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Table 7: Adverse events in the submitted trials providing adverse event data

	CVR	COC
Oddsson (2005b)		
	N = 512	N = 518
Any AE, n (%)	294 (57.6%)	281 (54.3%)
Headache, n (%)	97 (18.9%)	77 (14.8%)
Ring-related problems, n (%)	30 (5.9%)	0
Vaginitis, n (%)	54 (10.5%)	24 (4.6%)
Leukorrhoea, n (%)	26 (5.1%)	12 (2.3%)
Breast soreness, n (%)	17 (3.3%)	11 (2.1%)
Genital itch, n (%)	13 (2.5%)	5 (1.0%)
Acne, n (%)	4 (0.8%)	15 (2.9%)
Hypertension, n (%)	4 (0.8%)	8 (2.6%)
Weight gain, n (%)	13 (2.5%)	15 (2.9%)
Any SAE, n (%)	11 (2.1%)	7 (1.4%)
Deep Vein Thrombosis	1 (0.2%)	0
Discontinuation due to AE, n (%)*	58 (11.3%)	45 (8.7%)
Duijkers (2004)		
	N = 37	N = 40
Nausea, n (%)	6 (16.2%)	2 (5%)
Breast Tenderness, n (%)	2 (5.4%)	5 (12.5%)
Leukorrhoea, n (%)	2 (5.4%)	0
Vaginitis, n (%)	1 (2.7%)	2 (5%)
Headache, n (%)	2 (5.4%)	1 (2.5%)
Nervousness, n (%)	2 (5.4%)	0
Weight gain, n (%)	2 (5.4%)	0
	DMPA	NET-EN
Benagiano (1978)		
	N = 846	N = 832
"Registered some complaint"	60%	46%
Menstrual abnormalities	24.9%	19%
Headache	10.7%	6.9%
Abdominal discomfort	5.2%	3.1%
Anxiety/nervousness	3.9%	2.9%

Source: Constructed during the evaluation from published reports.

* For NuvaRing, the most frequent AEs leading to discontinuation were ring-related problems, leukorrhoea, headache, depression, vaginal discomfort and nausea. For COC, the most frequent AEs leading to discontinuation were headache, increased weight, decreased libido, hypertension, nausea, acne and depression.

AE = adverse event; COC = combined oral contraceptive; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; NET-EN = norethisterone enanthate; SAE = serious adverse event.

Extended assessment of harms

- 6.65 The submission noted that CVR has been widely available since 2001 and is approved in 71 countries, so safety data from this extensive clinical experience is available. This was provided in the Periodic Safety Update Report (PSUR) for NuvaRing, covering the period 2001 to 2024.
- 6.66 The PSUR data was particularly relevant to the risk of VTE. Clinical trials of hormonal contraceptives routinely exclude for ethical reasons women at high risk of VTE, and trials with one or two thousand participants would expect to see a minimal number of cases. The trial data submitted did not, therefore, address the question of the risk of VTE as an adverse event in CVR use.

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- 6.67 In the PSUR review of published data and case reports of VTE, three large studies were identified reporting rates of VTE with CVR vs COCs. The results are consistent with existing regulatory advice that etonogestrel is associated with a greater risk of VTE than levonorgestrel.⁴
- 6.68 Arterial thromboembolic events are much less common than VTE but carry a higher risk of mortality or serious morbidity. The PSUR reports that seven cases have been reported, which is too few to estimate relative risks.
- 6.69 Toxic shock syndrome (TSS) is a rare (< 1 case per 1,000,000 population per year) acute illness with fever, rash, hypotension and in some cases organ failure, caused by toxins produced by bacteria, especially *Staphylococcus aureus*. Many cases are associated with the use of tampons during menstruation, but menstrual cups and barrier contraceptives have also been identified as risk factors. The possibility that the CVR could also be a risk factor for TSS has been raised. The PSUR reports that short-term studies of vaginal flora and studies of the growth of *S. aureus* on CVR do not suggest that CVR creates conditions conducive to toxin production by *S. aureus*, and that no signal of increased risk could be identified from case reports.

Benefits/harms

- 6.70 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.71 The submission described CVR as non-inferior for the prevention of pregnancy compared to DMPA. This claim was not adequately supported; the evidence presented was of poor quality and unsuitable for the indirect treatment comparison on which the claim depended.
- 6.72 The submission described CVR as non-inferior in terms of safety compared to DMPA. This claim was not adequately supported, because the submitted data was of poor quality and unsuitable for the indirect treatment comparison on which the claim depended.
- 6.73 Taking into account the totality of the available data, including observational data from clinical use, it is reasonable to conclude that CVR is probably of similar efficacy and safety to DMPA. However, the clinical claim is of limited relevance, because DMPA was not the most appropriate comparator. Alternative comparators identified were COCs, to which, considering the totality of evidence, CVR is probably of similar efficacy and safety, and long-acting reversible contraceptives, to which CVR is very likely of inferior efficacy.
- 6.74 Overall, the PBAC considered that the claims of non-inferior comparative effectiveness and non-inferior safety were reasonable.

Economic analysis

6.75 The submission presented a cost minimisation approach to the economic analysis. The key inputs into the cost minimisation approach are listed in Table 8.

Table 8: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the submission, the effectiveness of the CVR is demonstrated to be non-inferior to DMPA with respect to unintended pregnancies at 5.5 – 24 months.
Therapeutic claim: safety	Based on evidence presented in the submission, the safety profile of CVR is demonstrated to be non-inferior to DMPA with respect to overall adverse events at 7.4 – 12 months.*
Evidence base	Indirect comparison of: <ul style="list-style-type: none"> randomised LEV 150/EE 30 OC-controlled trials (trial outcomes at 5.5-12 months with CVR and 12-24 months with DMPA) randomised NET-EN-controlled trials (trial outcomes at 7.4 months with CVR and 6-12 months with DMPA).
Equi-effective doses	12 week period: 3 CVR = 1 DMPA 150 mg/mL IM injection.
Direct medicine costs	Drug costs for 12 weeks (AEMP): CVR: 1 pack of 3 rings (AEMP = \$67.98) DMPA: 1 injection (AEMP = \$13.14) Compliance: CVR = 82.7% DMPA = 92.8% Annual drug costs: CVR: 4 packs of 3 rings = 12 rings (cost = \$271.92, assuming compliance of 82.7%*) DMPA: 4 injections (cost = \$48.78, assuming 92.8% compliance*)
Other costs or cost offsets	GP consultation (MBS item 23, Fee \$42.85): Initial CVR = 1 DMPA = 1 Annual number of HCP consultations for administration on Day 0 – 5 cycle CVR= 0 DMPA = 4.8 Bone mineral density scan (MBS item 12312/12315, Fee \$99.20 (85% benefit*)) CVR= 0 DMPA=Ongoing BMD scan required every 2 years (100% users) Additional qualitative benefits (indirect benefits) The following indirect benefits of CVR contribute to a broader cost-effectiveness profile to support a cost offset against DMPA of 6.1%: <ul style="list-style-type: none"> A rapid return to normal menstrual cycling after discontinuation (3 – 4 weeks), for women wanting to conceive compared to up to 18 months for DMPA users Lower pregnancy rating (Category B3) compared to DMPA (Category D) The 6.1% cost offset reflects these savings by accounting for fewer medical visits, reduced treatment costs for infertility, and diminished risks associated with neonatal care for conditions linked to unintended pregnancies with DMPA.

Source: Table 3.1.1, p121 of the submission main body.

AEMP = approved ex-manufacturer price; BMD = bone mineral density; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; EE = ethinylestradiol; GP = general practitioner; IM = intramuscular injection; LEV = levonorgestrel; MBS = Medicare Benefits Schedule; NET-EN = norethisterone enanthate OC = oral contraceptive.

*Added during evaluation

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- 6.76 The equi-effective doses were estimated as: CVR 3 rings \equiv DMPA 150 mg/mL, 1 injection, for every 12 weeks. These doses were based on the PI documents.
- 6.77 As shown in Table 8, the submission included a number of additional costs and cost-offsets in the analysis. These were:
- A difference in the number of health care practitioner consultations over a year of treatment, favouring CVR users;
 - A requirement for bone density scans for DMPA users, stated to be based on the DMPA PI;
 - A 6.1% cost offset against DMPA due to claimed additional indirect benefits of CVR, including lower foetal risk in unintended pregnancies and a faster return to fertility. This was calculated as 6.1% of the proposed approved ex-manufacturer price (AEMP) for CVR.
- 6.78 It is plausible that there would be a difference in health care practitioner consultations between DMPA users and CVR users. The submission proposed that a patient receiving DMPA would need to see a health care practitioner for each injection on Day 0-5 of a 28 day cycle and assumed that 18% of women would have to have a return visit for the first injection. The submission assumed that all visits would be with a GP. While the first visit for DMPA users might be with a GP it is also possible to obtain DMPA through nurse practitioner and midwife prescribing.
- 6.79 In at least one of the CVR trials (Gill, 2020), users could have the rings inserted by clinic staff and some made use of this option. CVR users may require additional visits with nurse practitioners or midwives as well. If individuals already have a valid prescription for DMPA and have it dispensed, they may also have DMPA administered by a nurse, and will not necessarily see a GP each time they have it administered.
- 6.80 A short consultation with a nurse practitioner is MBS item 82200, fee \$14.20, 85% benefit \$12.10; a 20 minute consultation is item 82210, fee \$58.85, benefit \$50.05. Follow-up DMPA injections would likely be charged at the lower fee. For midwives, the relevant MBS item number might be short or long postnatal visits (though this would be unlikely to include repeat visits): MBS items 82130 and 82135, fees and 85% benefits \$60.85; \$51.75 and \$124.50; \$105.85 respectively. Calculating the difference in health care consultations over 2 years might provide a more robust estimate of the difference between CVR users and DMPA users.
- 6.81 Similarly, it is also plausible that bone density scans may be ordered for some DMPA users, although dual-energy X-ray absorptiometry (DXA) has not been validated as a predictor of fracture risk in young women, so the results are difficult to interpret, and neither the American College of Obstetricians and Gynecologists nor the Royal College of Obstetricians and Gynaecologists recommend routine bone density scanning for

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women using DMPA.^{21,22} The rate of annual scans (9.5% of DMPA users) used in the analysis was not well supported. Further, there is no MBS item under which a young woman whose only risk factor for osteoporosis was DMPA use could have DXA (Item 12306 requires minimal-trauma fracture or proven low BMD; 12312 requires glucocorticoid use or excess or hypogonadism; 12315 requires hyperparathyroidism, liver disease, renal disease, malabsorption, rheumatoid arthritis or thyrotoxicosis; 12320 requires age >70 years; 12321 requires a change in treatment for established low BMD or minimal-trauma fracture; 12322 requires age >70 years). The ESC noted that patients using DMPA would not automatically meet the criteria for bone densitometry under the MBS, however some women in the proposed population for CVR may be eligible (e.g. those with a proven malabsorptive disorder).

- 6.82 Both of these costs should have been included at 80% of the MBS items, not 100%.
- 6.83 No evidence was presented to support the claimed cost offset of 6.1% of the annual AEMP with respect to the "additional indirect benefits". The results of the analysis as presented in the submission and as corrected during the evaluation are shown in Table 9.

²¹ 'Committee opinion no. 602: Depot medroxyprogesterone acetate and bone effects', (2014), *Obstet Gynecol* 123(6):1398-1402, available at www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2014/06/depot-medroxyprogesterone-acetate-and-bone-effects accessed 6 January 2025.

²² Faculty of Sexual & Reproductive Healthcare, (2019), 'Progestogen-only injectable contraception', Royal College of Obstetricians & Gynaecologists, available at www.fsrh.org/Common/Uploaded%20files/documents/progestogen-only-injectable-december-2014-amended-11july2023.pdf accessed 6 January 2025; the RANZCOG guidelines cited by the submission were based on the FSRH guidelines.

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Table 9: Results of the cost-minimisation approach

	DMPA	CVR	DMPA	CVR
			Corrected values*	
Pack size	1	3		
Max Quantity	1	1		
Max Repeats	1	3		
AEMP per Q12W	\$13.14	\$67.98		\$54.35
DPMQ per Q12W	\$27.59	\$86.55		\$71.90
GP consults/year	4.8	1		
GP Level B rebate (MBS item 23)	\$42.85	\$42.85	0.8*42.85=\$34.28	0.8*42.85=\$34.28
BMD scan (MBS item 12312/12315), 85% benefit	\$99.20	-	0	
Proportion of women who have BMD scan yearly	9.5%		0	
Adherence	92.8%	82.7%		
Total drug cost per year (AEMP)	\$48.78	\$271.92	\$48.78	\$217.38
Total MBS costs per year (GP consults)	\$206.60	\$42.85	\$165.28	\$34.28
Total MBS costs per year (BMD scans)	\$12.35	-	0	0
Cost offset for indirect economic benefits (6.1% of AEMP)	\$2.98	-	0.0%	
Total cost per year AEMP	\$267.72	\$267.72	\$214.05	\$214.05

Source: Table 3.2.2 p 125 and Attachment 9 of the submission main body.

AEMP = approved ex-manufacturer price; BMD = bone mineral density; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; DPMQ = dispensed price for maximum quantity; GP = General practitioner; MBS = Medicare Benefits Schedule; Q12W = every 12 weeks.

*Added during evaluation

- 6.84 The PSCR disagreed with the reduction of BMD scans from 9.5% to 0%, and cited results from an Australian retrospective cohort study (Dennerstein (2018)) which found 9.8% of patients using DMPA in a single Melbourne specialist's practice between 1981 and 2013 were referred for a DXA scan.
- 6.85 Dennerstein (2018) stated that DMPA was used for a range of conditions, including endometriosis, recurrent vaginal candidiasis, menstrual disorders and contraception; it was not used solely for the population included in the proposed restriction.
- 6.86 The ESC noted that the MBS GP Level B rebate was used in the cost-minimisation approach. It advised that while the Level B rebate would be used initially, once patients were established on treatment an MBS GP Level A consultation (MBS item 3, fee \$19.60) may be used.
- 6.87 The submission presented a sensitivity analysis, shown in Table 10, varying adherence to treatment and therefore the number of repeat prescriptions, number of health care practitioner visits, number of patients receiving BMD scans and the amount of the indirect cost offset. As shown in the corrected analysis as well as the sensitivity analysis, the main uncertainty relates to the number and cost of health care practitioner visits.

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Table 10: Sensitivity analysis - CMA

Scenario	Total cost per year per user	NuvaRing AEMP (3-pack)
Base case	\$267.72	\$67.98
Increase NuvaRing adherence from 82.7% to 87.4% (Oddsson 2005b)	\$267.72	\$64.32
Decrease NuvaRing adherence from 82.7% to 78.0% (Gill 2020)	\$267.72	\$72.07
Decrease NuvaRing number of repeats from 3 to 1 (which also increases number annual GP visits from 1 to 2)	\$267.72	\$55.03
Decrease annual proportion of DMPA users requiring BMD scan from 9.5% to 5%	\$263.31	\$66.64
Increase indirect cost offset from 6.1% to 10% of DMPA AEMP	\$269.63	\$68.55
Decrease indirect cost offset from 6.1% to 2% of DMPA AEMP	\$265.72	\$67.37

Source: Table 3.3.3 p126 of the submission main body.

AEMP = approved ex-manufacturer price; BMD = bone mineral density; DMPA = depot medroxyprogesterone acetate; GP = general practitioner.

- 6.88 No evidence was provided that the CVR provides a significant improvement in efficacy and/or reduction in safety over other hormonal contraceptives that are PBS-listed: DMPA, COCs, progestogen only pills, levonorgestrel IUD and etonogestrel implant.
- 6.89 The PSCR stated the sponsor would be open to considering an Unrestricted benefit listing for CVR, based on non-inferior safety and efficacy compared to EE/DRSP (Yaz, Yasmin), and would be willing to consider an AEMP of \$45.45 for 12 weeks of therapy (equivalent AEMP to EE/DRSP 3 x 28 tablets). The pre-PBAC response reiterated this, and stated that this would allow broader access to CVR.

Drug cost/patient/ year: \$312.76

- 6.90 The estimated drug cost/patient per year would be \$312.76 for NuvaRing pack of 3 rings, based on a DPMQ of \$71.90 derived from the corrected CMA shown in Table 9, and 4.35 prescriptions per year.

Estimated PBS usage & financial implications

- 6.91 This submission was not considered by DUSC.
- 6.92 The submission used a market share approach to estimate the likely use and financial impact of listing of CVR. The estimate of the market included both the current private market and medicines substituted on the PBS. Data sources used in the analysis are listed in Table 11.

Table 11: Key inputs for financial estimates

Parameter	Value applied and source	Comment*
Drug prices, Quantities, Item codes, indications, clinical setting	PBS online. Accessed from www.pbs.gov.au from Sept – Nov 2024	Appropriate.
PBS/RPBS utilisation data	PBS and RPBS utilisation statistics. Accessed from http://medicarestatistics.humanservices.gov.au/ from Aug - Nov 2024. To calculate patient beneficiary category distribution for DMPA in calendar year 2023. Dispensed unit trends 1992 – 2023 for DMPA.	Appropriate.

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Parameter	Value applied and source	Comment*																					
	3-year linear trend line for DMPA and OCs (2020 – 2023).																						
Commissioned utilisation data – persistence to DMPA	<p>Prospection data of 10% PBS sample (sourced October 2024).</p> <p>Dispensed PBS/RPBS volumes of DMPA between 2010 – 2024.</p> <p><u>DMPA persistence</u> At 2 years, 19% of DMPA users persist with treatment.</p>	Appropriate.																					
Market for CVR Expected growth rate	<p>IQVIA sales data (sourced October 2024) and HCP Survey.</p> <p>Sales data of CVR (available via private script) between 2020 – 2024.</p> <p>Average number of women prescribed CVR in the past 6 months, per health care practitioner = 6.9.</p> <p>Expected prescription rate: 22.1 per prescriber per 6 months. i.e. expected growth rate of 220%.</p>	Sponsor assumption.																					
Uptake rate	<table border="1"> <thead> <tr> <th>Uptake from DMPA:</th> <th>Uptake from OCs:</th> <th>Uptake from CVR private market</th> </tr> </thead> <tbody> <tr> <td>Yr 1 2025 [redacted] %</td> <td>Yr 1: [redacted] %</td> <td>Yr 1: [redacted] %</td> </tr> <tr> <td>Yr 2 2026 [redacted] %</td> <td>Yr 2: [redacted] %</td> <td>Yr 2: [redacted] %</td> </tr> <tr> <td>Yr 3 2027 [redacted] %</td> <td>Yr 3: [redacted] %</td> <td>Yr 3: [redacted] %</td> </tr> <tr> <td>Yr 4 2028 [redacted] %</td> <td>Yr 4: [redacted] %</td> <td>Yr 4: [redacted] %</td> </tr> <tr> <td>Yr 5 2029 [redacted] %</td> <td>Yr 5: [redacted] %</td> <td>Yr 5: [redacted] %</td> </tr> <tr> <td>Yr 6 2030 [redacted] %</td> <td>Yr 6: [redacted] %</td> <td>Yr 6: [redacted] %</td> </tr> </tbody> </table> <p>Based on HCP survey</p>	Uptake from DMPA:	Uptake from OCs:	Uptake from CVR private market	Yr 1 2025 [redacted] %	Yr 1: [redacted] %	Yr 1: [redacted] %	Yr 2 2026 [redacted] %	Yr 2: [redacted] %	Yr 2: [redacted] %	Yr 3 2027 [redacted] %	Yr 3: [redacted] %	Yr 3: [redacted] %	Yr 4 2028 [redacted] %	Yr 4: [redacted] %	Yr 4: [redacted] %	Yr 5 2029 [redacted] %	Yr 5: [redacted] %	Yr 5: [redacted] %	Yr 6 2030 [redacted] %	Yr 6: [redacted] %	Yr 6: [redacted] %	<p>Likely underestimated. Assumes COC users would only switch due to unwanted effects – may not be correct. Varied in sensitivity analyses.</p> <p>Uptake of CVR private prescriptions varied in sensitivity analyses.</p>
Uptake from DMPA:	Uptake from OCs:	Uptake from CVR private market																					
Yr 1 2025 [redacted] %	Yr 1: [redacted] %	Yr 1: [redacted] %																					
Yr 2 2026 [redacted] %	Yr 2: [redacted] %	Yr 2: [redacted] %																					
Yr 3 2027 [redacted] %	Yr 3: [redacted] %	Yr 3: [redacted] %																					
Yr 4 2028 [redacted] %	Yr 4: [redacted] %	Yr 4: [redacted] %																					
Yr 5 2029 [redacted] %	Yr 5: [redacted] %	Yr 5: [redacted] %																					
Yr 6 2030 [redacted] %	Yr 6: [redacted] %	Yr 6: [redacted] %																					
Adherence rates	<p>Average of 82.7%.</p> <p>Based on published date, average of 2 studies (Gill 2020, Oddson 2005b).</p>	May be reasonable.																					
Grandfathered patients	Not applicable.	The submission incorrectly identified approximately [redacted] ¹ patients prescribed CVR in the private market as grandfather patients. The applicant expected that most of these patients would be eligible for PBS subsidised access and did not propose any specific grandfather listing.																					
Median duration of therapy	12 months, based on HCP survey	May be reasonable but unable to verify.																					
MBS item	<p>MBS item 23, GP Professional attendance, \$42.85</p> <p>Bone mineral density scan MBS item 12306/12315</p> <p>Fee \$116.65, Benefit \$99.20.</p>	<p>GP visits should not be included.</p> <p>BMD scans not appropriate as covered in para 6.81.</p>																					

Source: Table 4.1.1 pp128-129 of the submission main body. Table 4.1.2 p130 of submission main body.
 BMD = bone mineral density; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; GP = general practitioner; HCP = healthcare provider; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

*Added during evaluation

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

6.93 The analysis was based on the assumption that use of CVR will be restricted to a population unable to tolerate DMPA or oral contraceptives. This assumption was not

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reasonable. The submission also assumed a low rate of switch from current private market contraceptive users, for which data were not available. This assumption may also be likely to underestimate the total use of CVR.

6.94 The estimated use and total financial impact as presented in the submission is shown in Table 12.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated – current CVR users	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Number of scripts dispensed – current users	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Number of scripts switched from DMPA	■ ¹	■ ²	■ ²	■ ³	■ ³	■ ³
Number of scripts switched from current OC	■ ³	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Total number of scripts of CVR dispensed	■ ³	■ ³	■ ⁴	■ ⁴	■ ⁵	■ ⁵
Estimated financial implications of NuvaRing						
Cost to PBS/RPBS less copayments	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶
Estimated financial implications for DMPA and other OCs						
Cost to PBS/RPBS less copayments	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷
Net financial implications						
Net cost to PBS/RPBS	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶
Net cost to MBS/Services Australia/other	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷	-\$■ ⁷
Net cost to PBS/RPBS/MBS/Services Australia without GP visits or BMD cost savings*	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶

Source: Tables 4.2.2, 4.2.11, 4.3.3, 4.4.1, 4.5.2, pp 134, 142, 145, 146, 148 of the submission main body.
 BMD = bone mineral density; CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; GP = general practitioner; MBS = Medicare Benefits Schedule; OC = oral contraceptive; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

*Added during evaluation.

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 5,000 to < 10,000
- ³ 10,000 to < 20,000
- ⁴ 20,000 to < 30,000
- ⁵ 30,000 to < 40,000
- ⁶ \$0 to < \$10 million
- ⁷ net cost saving

6.95 The submission inappropriately included cost savings from reduced GP visits and BMD scan; the impact of removal of these costs is shown in Table 12.

6.96 At year 6, the estimated number of patients was 500 to < 5,000 and the total cost to the PBS/RPBS of listing CVR was estimated to be \$0 to < \$10 million. The total cost to the PBS/RPBS was estimated to be \$10 million to < \$20 million in the first 6 years of listing. The cost was due to the difference in price proposed for CVR compared to the comparators. The estimated use and cost were underestimated, given the likely use beyond the proposed restriction and the switch from other products not included in the estimates. These assumptions could not be corrected during the evaluation. The

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evaluation noted errors in the financial calculations provided in the submission and requested revised estimates.

6.97 The submission presented sensitivity analyses, varying uptake rates from current contraceptive users, the growth rate for CVR prescriptions and adherence. These results are shown in Table 13. A multivariate analysis would have been useful but the fundamental assumptions – restricted benefit and uptake primarily from DMPA – would need to be corrected first.

Table 13: Sensitivity analyses – net cost to Government

Net cost to PBS + RPBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	2026	2027	2028	2029	2030	2031
Base case	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Max uptake rate from DMPA increased from █% to █%	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Max uptake rate from DMPA decreased from █% to █%	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Max uptake rate from OCs increased from █% to █%	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Max uptake rate from OCs decreased from █% to █%	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Annual growth rate NuvaRing increased from 8% to 12% to account for more switches from private script OCs	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Annual growth rate NuvaRing decreased from 8% to 4% to account for fewer switches from private script OCs	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
CVR adherence increased 82.7% to 87.4% (Oddsson 2005b)	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
CVR adherence decreased 82.7% to 78.0% (Gill 2020)	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Uptake from CVR (via private script) increased to Yr 1 █%, Yr 2 onwards █%	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹

Source: Table 4.6.1, p150 of the submission main body.

CVR = contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; Max = maximum; OC = oral contraceptives; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr = year.

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

6.98 The PSCR provided revised financial estimates, which included a revised requested AEMP of \$54.35 for 12 weeks of treatment, revised script equivalence to COCs, a lowered annual growth rate from +8% to +4%, and removal of adherence rates. The revised estimates showed a net cost to the PBS of \$0 to < \$10 million over the first 6 years of listing, and provided a scenario analysis that if █% of women currently using CVR privately are eligible for the proposed PBS listing, the net cost to the PBS will be \$0 to < \$10 million over the first 6 years of listing.

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Table 14: Revised estimated financial implications

Net cost to PBS + RPBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	2026	2027	2028	2029	2030	2031
Base case: AEMP \$54.35 per Q12W, annual growth 4%	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Scenario analysis 1: AEMP \$54.35 per Q12W, annual growth 4%, only █% uptake from private script	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Scenario analysis 2: AEMP \$45.45 per Q12W, annual growth 4%	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹

Source: Table 3, p5 of the PSCR.

AEMP = approved ex-manufacturer price; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Q12W = every 12 weeks.

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

6.99 The PSCR and pre-PBAC Response estimated that if CVR has an AEMP of \$45.45 and an unrestricted listing, the cost to the PBS will be \$0 to < \$10 million over the first 6 years of listing.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of etonogestrel with ethinylestradiol (ENG/EE) contraceptive vaginal ring (CVR) as a General Schedule Unrestricted Benefit. The PBAC’s recommendation for listing was based on its assessment that the cost-effectiveness of ENG/EE CVR would be acceptable if it were cost-minimised against the PBS-listed combined oral contraceptives (COCs) drospirenone with ethinylestradiol (EE/DRSP).
- 7.2 The PBAC noted that the submission nominated depo-medroxyprogesterone acetate (DMPA) injection as the main comparator and COCs as alternative comparators. The PBAC considered that there were a number of appropriate comparators, including recently PBS-listed COCs containing EE/DRSP.
- 7.3 The PBAC noted that a Restricted Benefit listing had been proposed in the submission. The PBAC considered that evidence provided in the submission did not support the proposal to restrict ENG/EE CVR PBS eligibility to women who were seeking contraception but required a non-oral preparation due to difficulty swallowing tablets, gastrointestinal disturbances or malabsorption issues, or undesirable adverse effects with the use of oral contraceptives. The PBAC advised that use outside of the proposed restriction was likely.
- 7.4 The PBAC noted consumer comments that ENG/EE CVR will provide another contraceptive option for women, providing greater contraceptive choice for a range of reasons that included, but were broader than, those specified in the submission.

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The PBAC also noted consumer comments highlighting that PBS listing of ENG/EE CVR would improve affordability and accessibility of ENG/EE for many women, and increase equitable access. The PBAC recalled the outcomes from the oral contraceptives stakeholder meeting convened in October 2024, including that stakeholders stated that it was important to have a range of hormonal contraceptive options available on the PBS as choice of therapy can be highly individualised. The PBAC therefore considered that listing ENG/EE CVR as an Unrestricted Benefit provided another contraceptive option for individuals.

- 7.5 The PBAC noted the limitations of the evidence that was submitted in support of the claim that ENG/EE CVR had non-inferior efficacy and safety compared to DMPA. The PBAC noted the evidence provided in support of the claim that ENG/EE had non-inferior efficacy and safety compared to COCs. The PBAC noted the comparison of adverse events between ENG/EE and COCs based on the evidence provided, and the limitations of this evidence that were identified. Overall, the PBAC considered that ENG/EE CVR has non-inferior contraceptive efficacy and safety compared to DMPA injection and COCs currently PBS-listed. The PBAC considered the ENG/EE CVR would provide a contraceptive option for a broader population than the population who would be prescribed DMPA. The PBAC therefore recommended listing ENG/EE CVR on a cost-minimisation basis to EE/DRSP. The PBAC noted that three ENG/EE CVR provides 12 weeks of contraception. The PBAC advised the equi-effective doses are 12 week cycle of ENG 11.7 mg/EE 2.7 mg CVR \equiv 12 week cycle (equivalent to 3 x 28 day cycles) of EE 20 microgram/DRSP 3 mg / 12 week cycle of EE 30 microgram/DRSP 3 mg.
- 7.6 The PBAC advised that ENG/EE CVR is suitable for prescribing by nurse practitioners and endorsed midwives.
- 7.7 The PBAC noted that the estimated use and financial estimates provided in the submission were based on the proposed Restricted listing. However, revised financial estimates for an Unrestricted listing were provided in the PSCR and pre-PBAC response which estimated a net cost to the PBS/RPBS of \$0 to < \$10 million in the first year and a total of \$0 to < \$10 million over the first 6 years of listing.
- 7.8 The PBAC considered that the estimates for an Unrestricted listing, which included revised script equivalence to COCs, a lowered annual growth rate from +8% to +4%, and removal of adherence rates, were more reasonable. However, the PBAC advised that overall, there were uncertainties in the uptake rate from DMPA and COCs that are listed on the PBS, and therefore uncertainties in the financial implications of their listings. The PBAC recalled its request from its July 2024 meeting that a utilisation review of newer oral contraceptive pills listed on the PBS be conducted 2 years after their listing (paragraph 7.12, drospirenone with ethinylestradiol, Public Summary Document (PSD), July 2024 PBAC Meeting with November 2024 Addendum) and considered that ENG/EE CVR should be included in this request.
- 7.9 The PBAC recommended that ENG/EE CVR should not be treated as interchangeable with any other medicines currently listed on the PBS.

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- 7.10 The PBAC recommended that the Early Supply Rule should apply.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ENG/EE CVR is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over other COCs currently PBS listed, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ETONOGESTREL + ETHINYLESTRADIOL					
etonogestrel 120 microgram/24 hours + ethinylestradiol 15 microgram/24 hours vaginal drug delivery system, 3 rings	NEW	1	3	3	NuvaRing
Restriction Summary [new1] / Treatment of Concept: [new1A]					
Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Midwives					
Restriction type: <input checked="" type="checkbox"/> Unrestricted benefit					

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.