

5.07 DROSPIRENONE, Pack containing 24 tablets 4 mg and 4 inert tablets, Slinda[®], Besins Healthcare Australia Pty Ltd

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Unrestricted benefit listing for the contraceptive drospirenone 4 mg tablets (Slinda[®], drospirenone from herein), an oral progestogen-only pill (POP).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis (break-even), specifically the number of unintended pregnancies avoided for cost neutrality from a health system perspective, compared to levonorgestrel 30 microgram tablets (Microlut[®]) and norethisterone 350 microgram tablets (Noriday[®] 28-Day).

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

Component	Description
Population	Women requesting contraception
Intervention	Slinda (drospirenone 4 mg tablet)
Comparator	Microlut 28 (levonorgestrel 30 microgram tablet)
Outcomes	<ul style="list-style-type: none"> Pregnancy rate, measured using the Pearl Index. The Pearl Index is the pregnancy rate per 100 woman-years of exposure (the number of pregnancies divided by the number of women-years of exposure X 100) Safety, including bleeding patterns
Clinical claim	<p>For women requesting contraception, drospirenone is superior in terms of effectiveness (pregnancy rate) and safety (bleeding patterns), compared with levonorgestrel.</p> <p>In addition to the main clinical claim, drospirenone has the following benefits, compared to levonorgestrel, contributing to increased adherence and contraceptive efficacy:</p> <ul style="list-style-type: none"> Suppression of ovulation Increased missed-pill window of 24 hours for drospirenone versus 3 hours for levonorgestrel

Source: Table 1-1, p17 of submission of main body.

2 Background

- 2.1 As of 12 November 2023, drospirenone has been approved in 59 countries globally, 25 in Europe and in 34 non-European countries. Drospirenone was granted marketing authorisation by the United States Food and Drug Authority (US FDA) on 23 May 2019. Drospirenone is reimbursed in five countries, including the United Kingdom (UK), Belgium, Finland, France and Norway. Drospirenone was also recently approved (April 2024) for reimbursement in Canada, with the condition that the cost of drospirenone does not exceed that of other POPs for contraception.¹

¹ Canadian Drug Agency, (2024), 'Drospirenone', accessed 1 August 2024. Available at: www.cadth.ca/drospirenone

- 2.2 The submission referred to the *National Women’s Health Strategy 2020-2030* and Priority Area 1 (Maternal, sexual and reproductive health). An action from this area is to remove barriers to support equitable access to timely, appropriate and affordable care for all women, including culturally and linguistically sensitive and safe care. This includes working towards universal access to sexual and reproductive health information, treatment and services that offer options to women to empower choice and control in decision-making about their bodies, including contraception. The submission stated that its request to list drospirenone on the Pharmaceutical Benefits Scheme (PBS) is aligned with this action.
- 2.3 The submission also referred to the inquiry into the universal access to reproductive healthcare that was referred to the Senate Community Affairs References Committee for inquiry and report. The submission noted that the report *Ending the postcode lottery: Addressing barriers to sexual, maternity and reproductive healthcare in Australia*² included a number of comments on the high financial costs of accessing contraceptives and a lack of access to a number of oral contraceptives on the PBS (including newer oral contraceptives). The submission also referred to the following recommendations made by the committee:
- Recommendation 4: The committee recommends that the Australian Government reviews, considers and implements options to make contraception more affordable for all people.
 - Recommendation 6: The committee recommends that the Department of Health and Aged Care and the Pharmaceutical Benefits Advisory Committee (PBAC) work with the pharmaceutical industry to consider options to improve access to a broader range of hormonal contraceptives that are not currently PBS subsidised, including newer forms of the oral contraceptive pill.
- 2.4 From July 2024, appropriately trained community pharmacists in Queensland will be authorised to prescribe hormonal contraceptives, including POP, as part of a pilot program.³ In addition, there are ongoing pilot programs in New South Wales, South Australia, Victoria, Australian Capital Territory, Western Australia and Tasmania, which allow trained pharmacists to resupply oral contraceptive pills to eligible

² The Senate, Community Affairs Reference Committee, (2023), ‘Ending the postcode lottery: Addressing barriers to sexual, maternity and reproductive healthcare in Australia’, Commonwealth of Australia, www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/ReproductiveHealthcare/Report

³ Queensland Government, (2024), ‘Changes to make it easier for Queensland women to access contraceptives’, accessed 1 August 2024. Available at: <https://statements.qld.gov.au/statements/99941>

women.^{4,5} These initiatives align with the priorities and actions stated in the *National Women's Health Strategy 2020-2023*, which is to improve access to and uptake of appropriate contraceptive methods through expansion of service provision.⁶

Registration status

- 2.5 Slinda was Therapeutic Goods Administration (TGA) registered on 5 July 2021, and is indicated for contraception.
- 2.6 The recommended dose is one tablet taken daily, at about the same time each day, for 28 consecutive days (one white active tablet taken daily during the first 24 days, and one green inactive tablet taken daily during the following 4 days).

Previous PBAC consideration

- 2.7 Drospirenone 4 mg tablet (hereafter referred to as drospirenone) has not been previously considered by the PBAC.
- 2.8 The PBAC recommended the listing of drospirenone with ethinylestradiol (drospirenone 3 mg with ethinylestradiol 20 microgram (Yaz[®]) and drospirenone 3 mg with ethinylestradiol 30 microgram (Yasmin[®])) at the July 2024 meeting. The PBAC considered that Yaz and Yasmin did not provide significant benefits in terms of greater efficacy or reduction in toxicity compared to other PBS-listed COCs.

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 with strikethrough.

⁴ New South Wales Health, (2024), 'FAQs: The oral contraceptive pill and the NSW Pharmacy Trial', accessed 5 September 2024. Available at: www.health.nsw.gov.au/pharmaceutical/Pages/pharmacy-trial-faq-ocp.aspx

⁵ Tasmanian Government Department of Health, (2024), 'Resupply of the oral contraceptive pill', accessed 5 September 2024. Available at: www.health.tas.gov.au/health-topics/sexual-and-reproductive-health/reproductive-health/contraception-fertility-control/resupply-oral-contraceptive-pill

⁶ Department of Health and Aged Care, (2023), 'National Women's Health Strategy 2020–2030', accessed 1 August 2024. Available at: www.health.gov.au/resources/publications/national-womens-health-strategy-2020-2030?language=en

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DROSPIRENONE					
Drospirenone 4 mg tablet, 112 [4 x 28] drospirenone 4 mg tablet [24] (& inert substance tablet [4], 4 x 28	\$	1	4	2	Slinda
Restriction Summary: Unrestricted / Treatment of Concept: NEW					
Concept ID (for internal Dept. use)	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				

- 3.2 The submission requested a General Schedule Unrestricted benefit listing, consistent with the current PBS listings for Microlut 28 and Noriday 28 Day. The submission requested an approved ex-manufacturer price (AEMP) of \$ | for drospirenone 112 tablets.
- 3.3 The submission requested that medical practitioners, nurse practitioners and midwives be included as authorised prescribers for drospirenone if listed on the PBS. This is consistent with the PBS listing for Microlut 28. The current listing for Noriday 28 Day includes medical practitioners and nurse practitioners.
- 3.4 The submission requested drospirenone 4 mg tablets be listed with a maximum quantity of 112 tablets (4 x 28) and a maximum of 2 repeats. The recommended dose for drospirenone is one tablet daily (one white active tablet taken daily during the first 24 days, and one green inactive tablet taken daily on the following four days). The requested maximum quantity and repeats is sufficient to provide treatment for approximately 12 months. It also aligns with the current PBS listings for Microlut 28 and Noriday 28 Day, which have a maximum quantity of 4 x 28 tablets and 2 repeats.

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

4 Population and disease

- 4.1 Contraception is intended to minimise unintended pregnancies and pregnancy terminations, and to improve sexual health. In Australia, approximately one in four women experience an unintended pregnancy during their lifetime, with higher incidences among women who are younger, First Nations, or socioeconomically disadvantaged, and those in rural areas. Unintended pregnancies have significant negative physical, mental, economic and social implications, with a total cost of \$7.2 billion of direct and indirect costs to the Government, women, carers, employers and the society. Empowering choice and control in reproductive decisions, including the use of contraception, is essential in family planning and a key foundation of the *National Women’s Health Strategy 2020-2030*.

- 4.2 Contraceptive choice is dependent on personal characteristics and reproductive history.⁷ Contraceptives available in Australia include combined oral contraceptives (COC), POP, intrauterine device, implants, injections, vaginal ring, barrier methods and sterilisation.
- 4.3 According to the Therapeutic Guidelines, POPs are an option for a woman who wishes to use oral contraception and has a contraindication to estrogen in COC.
- 4.4 POPs are contraindicated for use in individuals with current breast cancer. Situations that require expertise or referral include individuals with: unexplained vaginal bleeding that is a suspected serious condition, prior to investigation of the cause; previous breast cancer; severe (decompensated) cirrhosis; hepatocellular adenoma or malignant liver tumour; ischaemic heart disease, stroke or transient ischaemic attack that occurs while using a POP.¹²
- 4.5 The trials CF111/301 and CF111/302 excluded breastfeeding woman and those under 18 years of age.⁸
- 4.6 Drospirenone is a newer generation POP which provides contraception primarily by ovulation suppression. Drospirenone increases the viscosity of the cervical mucus and exerts progestational effects on the endometrium, with additional anti-androgenic and mild anti-mineralocorticoid effects. In addition, drospirenone has a longer missed-pill window of 24 hours which makes adherence easier to be achieved.

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

5 Comparator

- 5.1 The submission nominated levonorgestrel as the main comparator for the following reasons:
- Levonorgestrel was the most utilised POP according to PBS data from 2019-2023 and is therefore more likely to be replaced by drospirenone.
 - The TGA approved indication for levonorgestrel (oral contraception) is similar to drospirenone. The approved indication for norethisterone is an oral contraceptive for women who will not, or cannot tolerate other oral contraceptives or intrauterine devices. However, both levonorgestrel and norethisterone POPs are listed as Unrestricted benefit listings on the PBS.

⁷ The Faculty of Sexual and Reproductive Healthcare, (2016; amended 2019), 'UK Medical Eligibility Criteria for contraceptive use', accessed 1st August 2024. Available at: <https://ranzcog.edu.au/wp-content/uploads/2024/01/FSRH-Medical-eligibility-criteria-for-contraceptive-use.pdf>

⁸ Drouin D, (2014), 'A Pivotal, Multicenter, Double-Blind, Double-Dummy, Randomised Trial on the Contraceptive Efficacy, Tolerability and Safety of LF111 (Drospirenone) Over 9 Cycles in Comparison with Desogestrel 0.075 mg'.

- 5.2 There was inconsistency in the use of the comparator throughout the submission: levonorgestrel was nominated as the main comparator in clinical evaluation, while norethisterone was used in the economic evaluation. This approach may be conservative given the therapeutic equivalency between the two drugs and the lower cost of norethisterone compared to levonorgestrel. According to Therapeutic Relativity Sheets, all oral contraceptives are considered of similar utility and equivalent for pricing purposes, despite differences in active ingredients, strength and formulations. The PBAC considered the comparators to be appropriate.
- 5.3 The trials CF111/301 and CF111/302 indicated that POP is a suitable option for women who are intolerant to or contraindicated to estrogen in COC.¹³

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician highlighted the need to have a range of hormonal contraceptive options available on the PBS, and that patients' contraceptive needs will often change throughout their life. The clinician noted that there is a lack of newer oral contraceptive pills available on the PBS, and stated that drospirenone offers several advantages compared to oral contraceptive pills currently PBS-listed. This included the longer missed-pill window available with drospirenone compared to other POPs, and the option of another POP for patients unable to take estrogen-containing pills. The clinician stated that while a number of women are currently using drospirenone on the private market, making it available on the PBS would make it accessible to more women, and address equity and access issues that currently occur with this medicine. The PBAC noted the input provided in the sponsor hearing raised similar issues that had been highlighted in other forums, such as the report for the inquiry into the universal access to reproductive healthcare that was referred to the Senate Community Affairs References Committee, and the outcomes of the oral contraceptives stakeholder meeting held in October 2024.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (17), health care professionals (8) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with drospirenone. Health professionals commented that drospirenone has a range of clinical benefits in addition to effective contraception, including benefits for heavy menstrual bleeding, dysmenorrhoea, endometriosis, menstrual-related migraine, and for women who experience adverse effects or have contraindications to estrogen-containing contraceptives. Other benefits included that drospirenone was better tolerated compared to other progestogens and had a longer missed-pill window so there was less dependence on taking a pill at a particular time. Health professionals and

organisations noted the higher cost of drospirenone compared to other POPs was a barrier to patients accessing this medicine, and individuals also highlighted that the high cost of drospirenone was a disadvantage. Similarly, input from individuals noted there were health advantages to using drospirenone in addition to contraception, including improvements in menstrual pain, endometriosis and migraines leading to better quality of life and daily functioning (including work productivity), and fewer adverse effects compared to other hormonal contraceptive pills.

- 6.3 The PBAC noted the comments received from SPHERE Centre for Research Excellence, stating the drospirenone can be a useful contraceptive option in certain situations due to additional the clinical benefits it provided, and can also be useful for women of older reproductive age due to its benefits in relation to bleeding control and not containing estrogen, so it can be used in situations where estrogen-containing contraceptives are contraindicated or not appropriate. The Women’s Health & Research Institute of Australia stated that patients with migraines (including menstrual migraines) and at risk of blood clots or stroke have limited contraceptive options, and drospirenone provides another option for these patients.

Clinical trials

- 6.4 In the absence of a head-to-head trial comparing drospirenone to levonorgestrel for contraception, the submission was based on an indirect treatment comparison (ITC) between a pooled analysis of two drospirenone trials (CF111/301 and CF111/302) and one levonorgestrel trial (Korver 1998), using desogestrel as a common comparator.
- 6.5 Notably, CF111/302, a phase III double-blinded, randomised controlled trial (RCT), was designed to present pooled efficacy results with CF111/301, a phase III non-comparative trial, to meet the European Medicines Agency (EMA) study size requirements for evaluating the efficacy of steroid contraceptives.⁹
- 6.6 Details of the trials presented in the submission are provided in Table 2.

⁹ European Medicines Agency (EMA), (2005), ‘Guideline on clinical investigation of steroid contraceptives in women’, accessed 1 August 2024. Available at: www.tga.gov.au/sites/default/files/2024-06/guideline-clinical-investigation-steroid-contraceptives-women-ema.pdf

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CF111/301 (EUCTR2010-021787-15)	A Pivotal, Multicenter, Non-Comparative Trial on the Contraceptive Efficacy, Safety and Tolerability of Drospirenone as LF111 During 13 Cycles. Archer DF, Ahrendt HJ, Drouin D. Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability.	13 June 2014 Contraception 2015;92(5):439-44.
CF111/302 (EUCTR2011-002396-42)	A Pivotal, Multicenter, Double-Blind, Double-Dummy, Randomised Trial on the Contraceptive Efficacy, Tolerability and Safety of LF111 (Drospirenone) Over 9 Cycles in Comparison with Desogestrel 0.075 mg. Palacios S, Colli E, Regidor PA. Multicenter, phase III trials on the contraceptive efficacy, tolerability and safety of a new drospirenone-only pill.	10 July 2014 Acta Obstetricia et Gynecologica Scandinavica 2019; 98(12):1549-1557.
Korver 1998	Korver M. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill.	Eur J Contracept Reprod Health Care 1998;3(4):169-78.

Source: Table 2-7, pp52-53 of the submission main body.

6.7 The key features of the trials are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)
Drospirenone					
CF111/301	713	OL, MC, phase III 13 cycles	Moderate ^a	healthy women at risk of pregnancy, 18-45 years old	Overall PI, Method Failure PI, PI after correction for additional contraception and sexually active cycles, Overall and Method Failure pregnancy ratios, PI for subgroups ≤ 35 years old, Safety
Drospirenone vs desogestrel					
CF111/302	1,190; Drospirenone=858 Desogestrel ^c =332	R, DB, MC, phase III 9 cycles	Low	healthy women at risk of pregnancy, 18-45 years old	Overall PI, Method Failure PI, PI after correction for additional contraception and sexually active cycles, Overall and Method Failure pregnancy ratios, PI for subgroups ≤ 35 years old, Safety
Levonorgestrel vs desogestrel					
Korver 1998	1,306; Levonorgestrel=979 Desogestrel ^c =327	R, DB, MC 13 cycles	Moderate ^b	healthy women at risk of pregnancy, 18-45 years old	Overall PI, Overall PI excluding breastfeeding, Adjusted PI, Safety

Source: Table 2-9, pp59-61, Table 2-10, p61; Table 2-12, pp62-63; Table 2-14, p64; Table 2-19, p69 of the submission main body.

DB = double blind; MC = multi-centre; N = number of study participants; OL = open label; PI = Pearl Index; R = randomised.

^a Moderate risk of bias in confounding, participant selection, missing data and measurement of outcome, based on ROBINS-1.

^b Moderate risk of bias in reporting; uncertain risk of bias in method of randomisation and blinding of outcome assessments, based on Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

^c Desogestrel was the common comparator

6.8 The submission identified a single arm study, CF111/303, but this was excluded from the pooled analysis due to differences in trial populations, such as age and body mass index (BMI) > 30 kg/m². Excluding CF111/303 may not be reasonable given the trial participant characteristics were similar to the Australian population (refer to

paragraph 6.18 for more details). Drospirenone received FDA approval based on the results from CF111/303, which was conducted in the US.¹⁰

- 6.9 The Pre-Sub-Committee Response (PSCR) argued that it was reasonable to exclude CF111/303 from the clinical evaluation as it was conducted in the US for the purpose of fulfilling FDA requirements. The PSCR further argued that it was a single arm trial and therefore did not facilitate an anchored ITC vs levonorgestrel and was not considered suitable to pool with CF111/301 and CF111/302 based on differences in trial population. However, the ESC considered that CF111/303 may be representative of individuals using drospirenone in practice, as it included more participants who were obese (35% vs 6%) and with a higher blood pressure on entry (< 159/99 mmHg vs < 140/90 mmHg) than the other included studies. The ESC also noted the relevance of this, given that obesity has an impact on the efficacy of POPs.
- 6.10 The submission also identified a non-comparative trial, CF111/304, but it was excluded as it only assessed tolerability, safety and acceptability of drospirenone in females aged 12 to 17 years. Excluding CF111/304 may not be reasonable as the proposed listing does not restrict usage among adolescent females.
- 6.11 The key differences between the trials that may impact the results were:
- The treatment duration in the noncomparative trial CF111/301 and Korver 1998 RCT was 13-cycle, whereas it was 9-cycle for RCT CF111/302. The impact of using studies with different designs and treatment duration on the pooled analysis and ITC was uncertain.
 - CF111/301 and CF111/302 excluded breastfeeding women, those younger than 18 years of age and those with venous thromboembolism (VTE), while Korver 1998 included breastfeeding participants (30% of the trial population). Appropriately, the submission presented an additional ITC excluding breastfeeding patients from Korver 1998.
 - In CF111/301, 43% participants were indirect switchers (defined as a gap > 2 days and ≤ 4 months without oral contraceptive) from another oral contraceptive to drospirenone. In contrast, only 4% of the participants in CF111/302 were indirect switchers from another oral contraceptive to drospirenone or desogestrel. Around 36% of the participants in Korver 1998 were switchers; however, it was unclear whether they were direct switchers (with no break between previous contraception to levonorgestrel/desogestrel) or indirect switchers.
 - The treatment discontinuation rates were higher in the levonorgestrel group in Korver 1998 (39%), compared to drospirenone groups in CF111/301 (25%) and CF111/302 (18%).

¹⁰ Food and Drug Administration (FDA), (2022), 'Prescribing information', accessed 6 August 2024. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2022/216285s000lbl.pdf

- Method Failure Pearl Index (PI) in CF111/301 and CF111/302 was defined differently from the Adjusted PI in Korver 1998 (refer to paragraph 6.17 for more details), and thus the results cannot be compared between the trials.

Comparative effectiveness

6.12 The primary outcome presented in the submission was Overall PI, defined as the pregnancy rate per 100 woman-years of exposure (the number of pregnancies divided by the number of women-years of exposure x 100).

Table 4: Results of Overall PI across the trials

Trial ID	Drospirenone		Levonorgestrel		Desogestrel		Mean difference with common comparator desogestrel
	Number of pregnancy, n / N (%)	Overall PI (95% CI)	Number of pregnancy, n / N (%)	Overall PI (95% CI)	Number of pregnancy, n / N (%)	Overall PI (95% CI)	
CF111/301	3/713 (0.4)	0.51 (0.11,1.49)	NA	NA	NA	NA	NA
CF111/302	5/858 (0.6)	0.97 (0.32,2.27)	NA	NA	1/332 (0.3)	0.52 (0.013,2.91)	0.45# (NA)
Pooled analysis	8/1571 (0.5)	0.73 (0.31,1.43)	NA	NA	1/332 (0.3)	0.52 (0.013,2.91)	0.20 (0.18,0.22)
Korver 1998	NA	NA	4/331 (1.2)	1.55 (0.42,3.96)	3/989 (0.3)	0.41 (0.085,1.20)	1.14 (1.07,1.21)
			3*/NR (0.9)	1.41* (0.29,4.11)	1*/NR (0.1)	0.17* (0.004,0.93)	1.23* (1.17,1.31)
Indirect comparison of drospirenone vs levonorgestrel							-0.94 (-1.01, -0.86)
Indirect comparison of drospirenone vs levonorgestrel (excluding breastfeeding women in Korver 1998)							-1.04 (-1.11, -0.97)
Indirect comparison of drospirenone (using result from CF111/302 only) vs levonorgestrel (Korver 1998)							-0.69# (NA)

Source: Table 2-25, p76; Table 2-30, p79; Table 2-51, p100; Table 2-52, p100 of the submission main body

CI = confidence interval; n = number of participants reporting data; N = total participants in group; NA = not available; NR = not reported; PI = Pearl Index

#added during evaluation

* Exclude breastfeeding participants in Korver 1998. Approximately one third of participants in each group were breastfeeding when the study began, however exact numbers of participants who were breastfeeding were not provided.

6.13 The submission suggested that an Overall PI of ≤ 1 was defined as the threshold for highly effective contraceptive efficacy, based on the Clinical Trial Facilitation Group (CTFG).¹¹ The Overall PIs for drospirenone in CF111/301, CF111/302 and the pooled analysis were < 1 , indicating effective contraception. The ESC noted that drospirenone trials met the threshold for highly effective contraceptive efficacy, but the levonorgestrel trial did not. However, the ESC also noted that results of the overall PI did not include results from CF111/303.

¹¹ Clinical Trial Facilitation Group, (2014), 'Recommendations related to contraception and pregnancy testing in clinical trials', accessed 1 August 2024. Available at: www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

- 6.14 According to the EMA Guideline on Clinical Investigation of Steroid Contraceptives, if the difference between the point estimate and the upper limit of the 95% confidence interval (CI) is less than 1, the study is considered precise and reliable.¹⁴ As presented in Table 4, this criterion was met by CF111/301, but not by CF111/302 or Korver 1998 trials. The pooled results from CF111/301 and CF111/302, with an overall PI of 0.73 (upper limit of 1.43), met the EMA requirement.
- 6.15 ITC results showed a mean difference of -0.94 in Overall PI between drospirenone and levonorgestrel. However, the clinical significance of this difference was uncertain due to lack of a defined minimally clinically important difference (MCID) identified for relative Overall PI. The ESC considered it was unclear whether a reduction in Overall PI of 0.94 was clinically meaningful.
- 6.16 The mean difference in Overall PI between drospirenone (using CF111/302 only) and levonorgestrel was -0.69, which was different from the results obtained using pooled analysis, as mentioned in paragraph 6.15.
- 6.17 The Method Failure PI for drospirenone was 0.64 (95% CI: 0.13, 1.87) in CF111/301 and 1.40 (95% CI: 0.45, 3.27) in CF111/302. Korver 1998 reported an Adjusted PI of 1.41 (95% CI: 0.29, 4.12) for levonorgestrel. The Method Failure PI in drospirenone trials was defined as perfect medication cycles and sexual activity cycles without additional contraception, and regular intake of drospirenone/desogestrel as recorded in the e-diary. In contrast, Korver 1998 did not report perfect medication cycles and used an Adjusted PI that excluded pregnancies due to gross non-compliance. It was unclear if the Adjusted PI in Korver 1998 excluded pregnancy or treatment cycle associated with concomitant contraceptive use, potentially biasing the results in favour of levonorgestrel and desogestrel.
- 6.18 There were potential applicability issues to the Australian setting, as described below:
- Based on Therapeutic Guidelines, POP is the preferred hormonal method in breastfeeding. Of note, when breastfeeding participants from the Korver 1998 trial were excluded in the ITC, the mean difference in Overall PI between drospirenone and levonorgestrel was -1.04.
 - In Australia, approximately 31% women are obese, with a body mass index (BMI) > 30 kg/m².¹² In CF111/303, where 35% of the study population was obese with a mean BMI of 28.5 kg/m², the reported Overall PI was 2.9. This was higher than the values reported in pooled and individual CF111/301 and CF111/302 studies.¹³
- 6.19 The submission did not present outcomes related to the clinical claims of ovulation suppression or the effects of a longer missed-pill window of 24 hours. Additionally, no

¹² Australian Institute of Health and Welfare, (2024), 'Overweight and obesity', accessed 7 August 2024. Available at: www.aihw.gov.au/reports/overweight-obesity/overweight-and-obesity/contents/overweight-and-obesity

¹³ Department of Health and Aged Care, (2024), SLINDA drospirenone 4mg ARTG ID 338904, accessed 5 August 2024. Available at: www.tga.gov.au/resources/artg/338904

sensitivity analysis was presented for the excluded trial, CF111/303, which may be relevant to the Australian population.

- 6.20 The PSCR provided the results of a randomised study by Duijkers et al¹⁴ which looked at the impact of 24-hour delays in taking drospirenone, and found ovulation inhibition was maintained when there were four 24-hour delays in taking drospirenone throughout one cycle (24 days taking active tablets plus a 4 day pill-free interval). It claimed that drospirenone has the same flexibility as COC in terms of the safety window of missed pills while maintaining contraceptive reliability.
- 6.21 The ESC considered a sensitivity analysis including CF111/303 would be beneficial as this study included participants likely more representative of the Australian population.

Comparative harms

- 6.22 Table 5 summarises the key safety outcomes reported in CF111/302 and Korver 1998 trials.

¹⁴ Duijkers IJM, Heger-Mahn D, Drouin D, et al, (2016), 'Maintenance of ovulation inhibition with a new progestogen-only pill containing drospirenone after scheduled 24-h delays in pill intake', *Contraception* 93:4, pp303-9.

Table 5: Summary of safety outcomes in CF111/302 (TEAE) and Korver 1998 (AE)

TEAE	Drospirenone N=858 n (%)	Desogestrel N=332 n (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
CF111/302					
Participants with at least one TEAE	332 (38.7)	150 (45.2)	0.77 (0.59,0.99)#	0.86 (0.74,0.99)#	-6.49 (-12.80,-0.20)#
Acne	27 (3.1)	19 (5.7)	0.54 (0.29,0.98)#	0.55 (0.31,0.98)#	-2.58 (-5.30,0.20)#
Headache	38 (4.4)	17 (5.1)	0.86 (0.48,1.54)#	0.86 (0.50,1.51)#	-0.69 (-3.40,2.10)#
Nasopharyngitis	29 (3.4)	13 (3.9)	0.86 (0.44,1.67)#	0.86 (0.45,1.64)#	-0.54 (-2.90,1.90)#
Cervical dysplasia	26 (3.0)	11 (3.3)	0.91 (0.45,1.87)#	0.91 (0.46,1.83)#	-0.28 (-2.50,2.00)#
Vaginal haemorrhage	32 (3.7)	24 (7.2)	0.50 (0.29,0.86)#	0.52 (0.31,0.86)#	-3.50 (-6.60,-0.40)#
Participants with at least one TESAE	15 (1.7)	6 (1.8)	0.97 (0.37,2.51)#	0.97 (0.38,2.47)#	-0.06 (-1.70,1.60)#
Participants who prematurely terminated the trial due to TEAE	82 (9.6)	44 (13.3)	0.69 (0.47,1.02)#	0.72 (0.51,1.02)#	-3.70 (-7.80,0.40)#
AE	Levonorgestrel N=327 n (%)	Desogestrel N=979 n (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
Korver 1998					
Acne	13 (4.0)	30 (3.1)	1.31 (0.67,2.54)#	1.30 (0.68,2.46)#	0.91 (-1.50,3.30)#
Headache	20 (6.1)	73 (7.5)	0.81 (0.48,1.35)#	0.82 (0.51,1.32)#	-1.34 (-4.40,1.70)#
Dysmenorrhea	11 (3.4)	12 (1.2)	2.81 (1.23,6.42)#	2.74 (1.22,6.16)#	2.14 (0.10,4.20)#
Breast pain	10 (3.1)	39 (4.0)	0.76 (0.38,1.54)#	0.77 (0.39,1.52)#	-0.93 (-3.20,1.30)#
Vaginitis	9 (2.8)	37 (3.8)	0.72 (0.34,1.51)#	0.73 (0.36,1.49)#	-1.03 (-3.20,1.10)#
Nausea	5 (1.5)	32 (3.3)	0.46 (0.18,1.19)#	0.47 (0.18,1.19)#	-1.74 (-3.50,0)#
Serious AEs	6 (1.8)	14 (1.4)	1.29 (0.49,3.38)#	1.28 (0.50,3.31)#	0.40 (-1.20,2.00)#
Discontinuation due to AEs	30 (9.2)	103 (10.5)	0.86 (0.56,1.32)#	0.87 (0.59,1.28)#	-1.35 (-5.00,2.30)#

Source: Table 2-36, p82; Table 2-37, p83; Table 2-38, p84; Table 2-39, p85; Table 2-47, p95 of the submission main body.

AE = adverse event; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NA = not available; OR = odd ratio; RD = risk difference; RR = relative risk; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Bold indicates statistically significant results.

#added during evaluation.

6.23 The most common treatment-emergent adverse events (TEAEs) associated with drospirenone use, as reported in CF111/301, were acne (6.3%), headache (4.5%) and nasopharyngitis (3.1%). A total of 88 participants (12.3%) prematurely terminated the trial due to TEAEs. In CF111/302 study, the most common TEAEs associated with drospirenone were headache (4.4%), vaginal haemorrhage (3.7%), nasopharyngitis

(3.4%) and acne (3.1%). A total of 82 participants (9.6%) prematurely terminated the trial due to TEAEs. In Korver 1998, the most common adverse events (AEs) associated with levonorgestrel were headache (6.1%), acne (4.0%), dysmenorrhea (3.4%) and breast pain (3.1%). A total of 30 participants (9.2%) prematurely terminated the trial due to AEs. The ESC considered drospirenone to have a similar adverse effect profile to desogestrel.

6.24 Table 6 summarises the safety results based on the number of bleeding/spotting days in all three trials.

Table 6: Safety results on bleeding/spotting days in included trials

Cycle	Drospirenone		Levonorgestrel
	CF111/301 Mean days (SD)	CF111/302 Mean days (SD)	Korver 1998 Median days
Number of bleeding/spotting days			
Cycle 2-4 / RP1 ¹	13.4 (11.6)	13.1 (13.1)	17
Cycle 11-13 / RP4	8.2 (9.5)	NR	19
Number of bleeding days			
Cycle 2-4 / RP1 ¹	4.8 (6.7)	4.2 (6.1)	9
Cycle 11-13 / RP4	3.0 (5.2)	NR	11

Source: Table 2-56, p110 of the submission main body.

NR = not reported; RP1¹ = shifted 90-day reference period starting on Day 29; RP4 = 90-day reference period starting on Day 271; SD = standard deviation.

6.25 A claim of superior safety (in terms of bleeding patterns) with drospirenone, compared to levonorgestrel, was made by the submission, based on an unanchored comparison of patient-relevant bleeding outcomes from CF111/301, CF111/302 and Korver 1998. This was uncertain due to the use of different measures: mean days from CF111/301 and CF111/302 versus median days in levonorgestrel arm of Korver 1998. The PSCR argued that it is not unusual for safety outcomes to be excluded from ITCs, and that they are generally subject to inherent uncertainty as trials are generally underpowered for safety events. It argued that an unanchored comparison was considered most appropriate.

6.26 Unanchored comparison of bleeding outcomes suggests that participants on drospirenone experienced approximately four fewer bleeding or spotting days compared to levonorgestrel during cycles 2 to 4. However, the clinical significance is unclear, as bleeding or spotting patterns did not consistently favour drospirenone across all cycles.

6.27 The submission did not present ITC on safety between drospirenone and levonorgestrel.

Benefits/harms

6.28 On the basis of indirect evidence presented by the submission, approximately one unintended pregnancy would have been avoided for every 100 women years treated with drospirenone, in comparison to levonorgestrel, over a 9 to 13 cycles duration.

- 6.29 Excluding breastfeeding patients from Korver 1998 trial in the ITC, approximately one unintended pregnancy would have been avoided for every 100 women years treated with drospirenone, in comparison to levonorgestrel, over a 9 to 13 cycles duration.
- 6.30 Using data from only CF111/302 trial, approximately 0.70 unintended pregnancy would have been avoided for every 100 women years treated with drospirenone, in comparison to levonorgestrel, over a 9 to 13 cycles duration.
- 6.31 Additional harm could not be estimated because there was no comparative evidence presented of drospirenone vs levonorgestrel.

Clinical claim

- 6.32 The submission claimed that drospirenone was superior in terms of effectiveness (pregnancy rate) and safety (bleeding patterns), compared to levonorgestrel, for women requesting contraception.
- 6.33 Given the mechanism of action on ovulation suppression, drospirenone may be superior to levonorgestrel, but the magnitude of its relative effectiveness was uncertain because:
 - there were no head-to-head studies directly comparing the effectiveness of drospirenone and levonorgestrel; therefore, the evidence was based on ITC between a pooled analysis of two drospirenone trials (CF111/301 and CF111/302) and one levonorgestrel trial (Korver 1998), with desogestrel as a common comparator;
 - the transitivity assumptions of the ITC were affected by the heterogeneity in the included studies: CF111/301 was a single arm noncomparative trial, whereas CF111/302 and Korver 1998 were RCTs; women in CF111/302 received 9 treatment cycles compared with 13 cycles in CF111/301 and Korver 1998; and CF111/301 and CF111/302 excluded breastfeeding participants;
 - the submission excluded drospirenone CF111/303 trial from the ITC. The Overall PI was higher in that trial compared to the pooled results from CF111/301 and CF111/302 (2.9 versus 0.73); and
 - the submission did not provide a MCID for Overall PI, the primary efficacy outcome.
- 6.34 The PSCR argued that as POPs are immediately effective if taken within the first 5 days of the menstrual cycle, or if started at another time are effective after taking active pills for 7 consecutive days, the difference in the number of treatment cycles is unlikely to have a significant impact on the ITC results.
- 6.35 The PSCR acknowledged that the Korver 1998 study included individuals who were breastfeeding, whereas CF111/301 and CF111/302 excluded these participants, however claimed performing the ITC using the Overall PI and PI excluding breastfeeding individuals accounted for this and allowed a fair comparison. The PSCR

further claimed that in both analyses drospirenone was associated with an improvement in pregnancy rate compared to levonorgestrel.

- 6.36 The PSCR claimed there was no evidence of an accepted MCID for Overall PI from previous PBAC submissions, including that of Kyleena® (levonorgestrel) intrauterine drug delivery system (considered by the PBAC in March 2019), and stated that this appeared to be consistent with submissions for contraceptive agents reviewed by other health technology assessment agencies internationally. The PSCR further stated that a targeted literature search did not return any relevant results identifying an MCID.
- 6.37 The ESC considered that the claim that drospirenone had superior efficacy compared to levonorgestrel was plausible, however the magnitude of greater efficacy, was uncertain based on the ITC, transitivity issues, and the exclusion of CF111/303.
- 6.38 The submission described drospirenone as superior in terms of safety compared to levonorgestrel. However, the claim was not adequately supported because:
- it was based on an unanchored comparison of safety between drospirenone and levonorgestrel trials;
 - the differences in bleeding patterns may not be clinically significant; and
 - the bleeding patterns did not consistently favour drospirenone across all cycles.
- 6.39 The ESC considered there was a lack of evidence to support the claim that drospirenone had a superior safety profile compared to levonorgestrel, as the comparison was based on different outcomes (mean vs median days of bleeding), and the clinical significance of differences was unclear given that it was not consistently in favour of drospirenone.
- 6.40 The PBAC considered that the claim of superior comparative effectiveness was likely reasonable, however the magnitude of greater efficacy was uncertain.
- 6.41 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

Economic analysis

- 6.42 The submission presented a modified economic evaluation by estimating the number of unintended pregnancies needed for cost neutrality (break-even) from a health care system perspective. The purpose of this approach was to translate the superior efficacy of drospirenone (avoidance of unintended pregnancies) into cost savings and compare these savings to the incremental cost of drospirenone.
- 6.43 As stated in paragraph 5.2, while the submission nominated levonorgestrel as the main comparator, norethisterone was used in the economic evaluation due to its lower price. The ESC agreed that norethisterone was an appropriate comparator for the economic analysis. Although this approach was conservative, the incremental

pregnancies avoided per 100 woman-years of contraception, used in the economic evaluation, was based on the ITC comparing drospirenone with levonorgestrel.

- 6.44 The primary economic analysis was a break-even analysis on direct health costs, demonstrating the number of unintended pregnancies that need to be avoided per 100 women for drospirenone to be cost-effective. The submission also included additional analyses that presented a best case scenario based on clinical guidelines (refer to paragraph 6.45) and a worst case scenario based on evidence from a clinical trial setting (refer to paragraph 6.46), where compliance was expected to be better, to show the plausible range where drospirenone is cost-effective. The submission considered the true result to lie somewhere between the best- and worst-case scenarios presented.
- 6.45 The submission derived best-case scenario estimates from The Faculty of Sexual and Reproductive Healthcare (FSRH) guidelines, which suggest that typical use of POP could lead to a pregnancy risk of 90-99%.¹⁵ Consequently, the submission estimated that drospirenone might reduce the pregnancy risk by up to 9% compared to other POPs (99% vs. 90%) due to its mechanism of ovulation suppression and longer missed-pill window. However, this 9% reduction was uncertain, as it referred to the perfect use of POP, and not necessarily due to the improved mechanism of action.
- 6.46 The worst-case scenario was derived from the ITC results, as presented in paragraph 6.15, which estimated an incremental 0.935 unintended pregnancies avoided per 100 woman-years of contraceptive use. However, the ITC results were considered uncertain due to the transitivity issues among the trials, as highlighted in paragraph 6.11. Given this uncertainty, it would be more appropriate and conservative to consider the ITC results as representing the best-case scenario, while assuming non-inferiority in effectiveness between drospirenone and levonorgestrel or norethisterone as the worst-case scenario. The ESC considered the ITC should be considered the best-case scenario, and the worst-case scenario should assume non-inferior effectiveness.
- 6.47 The submission requested an AEMP of \$ [REDACTED] and dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] for drospirenone 4 mg 112 tablets (4 x 28 tablets).
- 6.48 The Impact of Unintended Pregnancy report estimated the total direct costs of 197,234 unintended pregnancies in Australia at \$2.2 billion, with indirect costs amounting to \$5 billion.¹⁶ Of the direct costs, 91% was borne by the Government, while 9% was borne by the women experiencing unintended pregnancies. Indexed to 2024 values, the average cost per unintended pregnancy was estimated to be \$42,060,

¹⁵ The Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists, (2024), 'FSRH CEU statement: Drospirenone 4mg progestogen-only pill', accessed 29 July 2024. Available at: www.fsrh.org/Common/Uploaded%20files/documents/fsrh-ceu-statement-drsp-pop-janu24.pdf

¹⁶ Organon and HTAnalysts, (2022), 'Impact of Unintended Pregnancy', accessed 29 July 2024. Available at: www.organon.com/australia/reports/

with direct health costs to the Government amounting to \$11,695. Notably, direct costs included expenses incurred due to miscarriages, stillbirths, abortions, and live births up to 12 months post-pregnancy whereas indirect costs included lost wages, income and Government parenting support payments. The estimated costs of unintended pregnancies were uncertain and possibly overestimated given the variation in coverage of abortion and miscarriage costs across different states and territories. The ESC considered there were substantial uncertainties in the estimated direct costs given the variations in coverage for abortion and miscarriage costs between states and territories, and considered the direct costs to be overestimated.

6.49 Table 7 summarises the results of the economic evaluation.

Table 7: Results of the economic evaluation

	Direct	Indirect	Total	Source
Total annual cost of unintended pregnancies (2020 Australian dollars)	\$2.2 billion	\$5 billion	\$7.2 billion	Based on Organon report (2022)
Number of unintended pregnancies in Australia 2020	197,234	197,234	197,234	Based on Organon report (2022)
Total one-year costs				
Cost of an unintended pregnancy 2020	\$11,154	\$25,351	\$36,505	Based on Organon report (2022)
Cost inflated to 2024 values				Calculation
Percentage of cost to Government	91%	13%	37%	Based on Organon report (2022)
Cost of an unintended pregnancy to Government 2020	\$10,150	\$3,296	\$13,507	Based on Organon report (2022)
Cost inflated to 2024 values				Calculation
Unintended pregnancies need to be avoided by drospirenone 4 mg per cohort of 100 women treated for one year				
Break even for Societal perspective	2.26	0.99	0.69	Calculation
Break even for Government perspective	2.48 ^a	7.65	1.87	Calculation

Source: Table 3-3, p115, Attachment 5 of the submission main body.

^a calculated as \$/█/\$█

6.50 The results of the economic evaluation were uncertain due to the limitations of the ITC outlined in paragraph 6.46.

6.51 From the Government perspective, the number of unintended pregnancies needed to break even, 2.48 per 100 woman-years for direct costs and 1.87 per 100 woman-years for total costs, was higher than the 0.935 unintended pregnancies avoided per 100 woman-years according to the ITC results. However, from the societal perspective, only 0.69 unintended pregnancies per 100 woman-years needed to be avoided to break even, which was lower than the ITC results. The submission stated that the results were conservative, as they do not account for potential quality-of-life benefits associated with a less restrictive dosing window or the consequences of unintended pregnancies. However, no evidence was provided regarding the quality-of-life benefits associated with a longer missed-pill window. The pre-PBAC response claimed that quality-adjusted life year (QALY) gains could come from multiple sources, including lower risk of unintended pregnancy which could impact both parents and extended family members, and peace of mind for the patient from a longer missed-pill window. The PBAC noted no data were provided to support the claim that a longer missed-pill window would result in quality-of-life benefits.

- 6.52 Using a cost-effectiveness analysis approach, with an incremental drug cost of \$ [REDACTED] and 0.935 additional unintended pregnancies per 100 women, the incremental cost-effectiveness ratio (ICER) would be \$25,000 to < \$35,000 per additional unintended pregnancy avoided. This ICER exceeds the estimated cost per unintended pregnancy of \$ [REDACTED], indicating that drospirenone is not cost-effective at the proposed dispensed cost.
- 6.53 For drospirenone to be cost-effective, with a cost per unintended pregnancy of \$ [REDACTED] and 0.935 additional unintended pregnancies per 100 women, the incremental drug cost should be \$ [REDACTED] (0.935 x \$ [REDACTED]) per 100-woman years. This equates to an incremental cost of approximately \$ [REDACTED] per year of treatment and \$ [REDACTED] per pack. On this basis, the ESC considered a cost of approximately \$ [REDACTED] per pack was likely reasonable.
- 6.54 Sensitivity analyses were conducted during evaluation to estimate the uncertainty around the incremental unintended pregnancies avoided with drospirenone compared to both levonorgestrel and norethisterone, as presented in Table 8.

Table 8: Sensitivity analyses conducted during evaluation

Analyses	Incremental cost	Incremental unintended pregnancy avoided	ICER	% change to ICER
Drospirenone vs levonorgestrel				
Base case ^a	\$ [REDACTED]	0.935	\$ [REDACTED] ¹	-
Using ITC results excluding breastfeeding participants	\$ [REDACTED]	1.029	\$ [REDACTED] ¹	- [REDACTED]%
Using ITC results based on CF111/302	\$ [REDACTED]	0.689	\$ [REDACTED] ²	[REDACTED]%
Drospirenone vs norethisterone				
Base case ^a	\$ [REDACTED]	0.935	\$ [REDACTED] ¹	-
Using ITC results excluding breastfeeding participants	\$ [REDACTED]	1.029	\$ [REDACTED] ¹	- [REDACTED]%
Using ITC results based on CF111/302	\$ [REDACTED]	0.689	\$ [REDACTED] ²	[REDACTED]%

Source: Attachment 5 of the submission.

ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison.

^aBase case was the ITC using pooled analysis of CF111/301 and CF111/302 versus Korver 1998

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$35,000 to < \$45,000

- 6.55 Excluding breastfeeding patients from the ITC results reduced the ICER by [REDACTED]%. In contrast, using efficacy data from CF111/302, which reported a lower incremental number of unintended pregnancies avoided, increased the ICER by [REDACTED]%.

Drug cost per patient per year: \$ [REDACTED]

- 6.56 The estimated drug cost/patient per year would be \$ [REDACTED], based on a DPMQ of \$ [REDACTED] and 3.26 prescriptions per year.
- 6.57 The drug cost/patient per year for norethisterone is \$63.35, based on a DPMQ of \$19.44 for 112 tablets and 3.26 prescriptions per year. The requested DPMQ for drospirenone results in an incremental cost of \$ [REDACTED] per woman per year. For a cohort of 100 women, this results in an incremental cost of \$ [REDACTED] per year.

Estimated PBS usage & financial implications

- 6.58 This submission was not considered by DUSC.
- 6.59 The submission used a market share approach to estimate the financial impact of listing drospirenone. The submission stated that listing drospirenone is expected to capture significant market share through two primary populations:
- (i) Population 1: substitution of PBS-listed POPs (levonorgestrel and norethisterone)
 - (ii) Population 2: transition of patients from private market of drospirenone to PBS/RPBS.
- 6.60 The key inputs and sources of data used in the financial estimates of listing drospirenone are presented in Table 9 below. The ESC considered that the estimated uptake rates in both patient groups was uncertain and not supported by evidence.

Table 9: Key inputs for financial estimates

Parameter	Value applied and source	Comment#
Population 1: Substitution of levonorgestrel and norethisterone on the R/PBS (Market share)		
Projected prescription volume of levonorgestrel	█ ¹ prescriptions in Year 1 to 6, based on the under copayment data for the year 2022-2023 from the R/PBS and assuming a growth rate of 0% based on R/PBS item statistic report for levonorgestrel (2913H).	The growth rate of 0% was uncertain. Additionally, the dataset for the under copayment data does not perfectly align with the calendar year used in the R/PBS statistics.
Projected prescription volume of norethisterone	█ ² in Year 1, decreasing to █ ³ in Year 6 based on the under copayment data for the year 2022-2023 from the R/PBS and assuming a percentage of -4.9% in Year 1 to -6.9% in Year 6 based on R/PBS item statistic report for norethisterone (1967M).	This was uncertain. The dataset for the under copayment data does not perfectly align with the calendar year used in the R/PBS statistics.
Substitution/uptake rate by drospirenone	Increase from 60% in Year 1 to 92.5% in Year 6, based on sponsor estimates and advice from clinicians.	This was uncertain; no data or evidence was provided to support the assumption.
Levonorgestrel	Published DPMQ: \$21.16 for 112-day supply.	This was reasonable.
Norethisterone	Published DPMQ: \$19.44 for 112-day supply.	This was reasonable.
Drospirenone	Requested DPMQ: \$█ for 112-day supply.	This was reasonable.
Population 2: Replacement of current drospirenone private market		
Projected number of women on drospirenone	█ ⁴ women in Year 1, increase to █ ⁵ women in Year 6, based on sponsor's data on private market usage between August 2021 to April 2024.	The was uncertain. There was approximately a 102% increase in prescriptions from 2022 to 2023. In addition, combined oral contraceptives with drospirenone and ethinylestradiol (Yaz and Yasmin) were recommended at the July 2024 PBAC meeting.
Uptake rate from private to R/PBS	75% in Year 1 to 100% in Year 2-6.	This was reasonable as it is cost saving to switch to R/PBS prescription, however, no data was provided to support the assumption.

Source: Table 4-4, p121, Table 4-6, p123 of the submission main body and Attachment 6 of the submission.

DPMQ = Dispensed price maximum quantity; PBAC = Pharmaceutical Benefits Advisory Committee; R/PBS = Repatriation Schedule of Pharmaceutical Benefits/Pharmaceutical Benefits Scheme.

#added during evaluation

The redacted values correspond to the following ranges:

¹ 100,000 to < 200,000

² 20,000 to < 30,000

³ 10,000 to < 20,000

⁴ 60,000 to < 70,000

⁵ 70,000 to < 80,000

6.61 Table 10 presents the estimated financial implications of listing drospirenone.

Table 10: Estimated use and financial implications

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Estimated extent of use						
Number of patients treated ^a	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
Number of scripts dispensed	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁵	█ ⁵
Estimated financial implications of drospirenone						
Cost to PBS/RPBS less copayments	\$█ ⁶	\$█ ⁶	\$█ ⁷	\$█ ⁷	\$█ ⁷	\$█ ⁷
Estimated financial implications for levonorgestrel and norethisterone						
Cost to PBS/RPBS less copayments	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸
Net financial implications						
Net cost to PBS/RPBS	\$█ ⁶	\$█ ⁶	\$█ ⁷	\$█ ⁷	\$█ ⁷	\$█ ⁷

Source: Table 4-8, p123, Table 4-9, p124, Table 4-11, p125 of the submission main body, Attachment 6 of the submission.

^a Calculated during evaluation as the number of scripts divided by 3.26 scripts per year.

The redacted values correspond to the following ranges:

¹ 80,000 to < 90,000

² 100,000 to < 200,000

³ 200,000 to < 300,000

⁴ 300,000 to < 400,000

⁵ 400,000 to < 500,000

⁶ \$20 million to < \$30 million

⁷ \$30 million to < \$40 million

⁸ net cost saving

6.62 The net cost to the Repatriation Schedule of Pharmaceutical Benefits/Pharmaceutical Benefits Scheme (R/PBS) of listing drospirenone was estimated to be \$20 million to < \$30 million in Year 1 (80,000 to < 90,000 patients), increasing to \$30 million to < \$40 million in Year 6 (100,000 to < 200,000 patients), with a total of \$100 million to < \$200 million in the first 6 years of listing.

6.63 The utilisation/financial estimates were considered uncertain due to the following reasons:

- For Population 1, the projected zero growth of levonorgestrel prescriptions and the declining trend of norethisterone scripts were uncertain.
- For Population 2, the projected number of women using drospirenone was uncertain. The utilisation of drospirenone was likely underestimated given the actual growth rate was 102% from 2022 to 2023 compared to the forecasted growth of 28% from 2023 to 2024. Furthermore, the forecast growth rate for the year 2024 was based on utilisation data from January to April 2024.
- The uptake rates of drospirenone for both the populations was uncertain, as the substitution rates were based on sponsor's assumptions with no supporting evidence.
- In addition, patients using other contraceptives (both PBS-listed and non-PBS listed) who may switch to using drospirenone if PBS-listed, are not accounted for in the estimates.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of drospirenone 4 mg tablets (Slinda) as an Unrestricted Benefit.
- 7.2 The PBAC noted comments from clinicians at the oral contraceptives stakeholder meeting and the sponsor hearing, and comments from health professionals and individuals in the consumer comments, highlighting the importance of having a range of contraceptive options available on the PBS so that cost is not a barrier to accessing the most appropriate option, noting that contraceptive requirements may change throughout life.
- 7.3 The PBAC noted the sponsor hearing and consumer comments stated that drospirenone offers advantages compared to other hormonal contraceptives currently PBS-listed, including having a longer pill-free window compared to other POPs, and providing an additional option for patients who cannot use estrogen-containing contraceptives. The PBAC also noted that drospirenone is currently available in the private market and comments stated that cost is a barrier to accessing drospirenone for some women.
- 7.4 The PBAC considered levonorgestrel was an appropriate clinical comparator. The PBAC considered that the submission's claim that drospirenone has superior efficacy compared to levonorgestrel is plausible, although the magnitude of superior efficacy is uncertain based on the ITC, transitivity issues, and the exclusion of CF111/303 in analyses. The PBAC noted a sensitivity analysis including CF111/303 as requested by ESC was not provided in the pre-PBAC response. The PBAC considered there was a lack of evidence to support the claim that drospirenone had superior safety compared to levonorgestrel, as different outcomes were used for comparison, and findings were not consistently in favour of drospirenone.
- 7.5 The PBAC considered norethisterone to be an appropriate economic comparator. The PBAC noted there were uncertainties in the economic evaluation, including that coverage of abortion and miscarriage costs vary between states and territories. The direct and indirect costs were generally considered to be over-estimated. The PBAC noted the submission claimed the economic evaluation was conservative and the pre-PBAC response stated that improvements in quality-of-life could come from multiple sources. However, the PBAC considered a cost-utility analysis would be required to adequately value quality-of-life impacts.
- 7.6 The PBAC noted the submission presented a break-even analysis on direct health costs as the primary economic analysis, and also included a 'best case' and 'worst case' scenario. The PBAC considered the best-case scenario should be the ITC, and the worst-case scenario should assume non-inferior effectiveness.
- 7.7 The PBAC considered that drospirenone provides an additional, different oral contraceptive option and offers benefits in certain clinical situations compared to PBS-listed oral contraceptives. The PBAC therefore recommended that an ex-manufacturer

price, consistent with the monthly ex-manufacturer cost recommended for ||||| would be acceptable (i.e. \$| for a 4 x 28 tablet pack).

- 7.8 The PBAC noted the financial estimates were based on uptake rates from two populations – patients currently using drospirenone on the private market and patients switching from other POPs. The PBAC considered these estimates to be uncertain and not supported by evidence. Based on the AEMP recommended by the PBAC in paragraph 7.7, and the sponsor’s model, the estimated net cost to the PBS/RPBS could range between \$70 million to < \$80 million over 6 years (based on only the private market population) and \$100 million to < \$200 million over 6 years (if uptake rates are from the two populations of patients switching from other POPs and patients using drospirenone on the private market).
- 7.9 The PBAC recommended that drospirenone should not be treated as interchangeable with any other drugs.
- 7.10 The PBAC advised that drospirenone is suitable for prescribing by nurse practitioners and authorised midwives.
- 7.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for drospirenone:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies, as there was a lack of evidence demonstrating superior safety, and uncertainty with regards to the magnitude of superior efficacy, of drospirenone over comparators;
 - b) The treatment is not expected to address a high and urgent unmet clinical need due to other hormonal oral contraceptive products being available;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 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
DROSPIRENONE					
drospirenone 4 mg tablet [24] (& inert substance tablet [4], 4 x 28	NEW MP NP MW	1	4	2	Slinda
Benefit Type New: Unrestricted					
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.