

5.07 ESTETROL WITH DROSPIRENONE, Pack containing 24 tablets estetrol 14.2 mg with drospirenone 3 mg and 4 inert tablets, Nextstellis[®], Mayne Pharma International Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Unrestricted Benefit listing for 14.2 mg estetrol (equivalent to 15 mg of estetrol monohydrate) with 3 mg drospirenone (Nextstellis[®]), a combined oral contraceptive (COC).
- 1.2 Listing was requested on the basis of a cost-consequence analysis (CCA), with disaggregated costs and a range of safety outcomes, versus other COCs currently listed on the Pharmaceutical Benefits Scheme (PBS).

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

Component	Description
Population	Women of reproductive age seeking a form of oral contraception
Intervention	Estetrol with drospirenone (E4/DRSP)
Comparator	Any fixed dose combined oral contraceptive available on the PBS
Outcomes	Primary outcome measure: Birth control or contraception Secondary outcome measures: Safety (improved thrombotic and myocardial infarction/stroke risk)
Clinical claim	For patients requiring combined oral contraception, E4/DRSP is non-inferior to other combined oral contraceptives in terms of efficacy of contraception/birth control and general safety. E4/DRSP is superior to both PBS-listed and the near market combined oral contraceptives in terms of specific longer-term safety such as risk of venous thromboembolism and the risk of myocardial infarction and stroke

Source: Table 1.1, p17 of the submission main body.

E4/DRSP = estetrol 15 mg/drospirenone 3 mg; PBS = Pharmaceutical Benefits Scheme.

2 Background

- 2.1 The submission referred to The Senate Community Affairs Reference Committee (2023) 'Ending the postcode lottery: Addressing barriers to sexual, maternity, and reproductive healthcare in Australia'. The submission noted the report stated the committee understood that certain newer oral contraceptive pills may be more appropriate for particular patients, have fewer negative side effects and can be effective in reducing androgen symptoms (e.g. acne and hirsutism). The submission also referred to the following recommendation made by the committee:

- "Recommendation 6: The committee recommends that the Department of Health and Aged Care and the Pharmaceutical Benefits Advisory Council (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.....”

- 2.2 The submission claimed it was aligned with the National Women’s Health Strategy 2020-2030¹ which aims to support ongoing improvement in the health and well-being of Australian women. One of the Strategy’s priorities is to increase access to sexual health and reproductive health care information, diagnosis, treatment and services.
- 2.3 One action for this priority is to remove barriers to support equitable access to timely, appropriate and affordable care for all women. 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, as well as improving access to and uptake of appropriate contraceptive measures.

Registration status

- 2.4 Estetrol with drospirenone (hereafter E4/DRSP) was Therapeutic Goods Administration (TGA) registered on 26 November 2021 for use by women of reproductive potential to prevent pregnancy.
- 2.5 The recommended dose is one tablet taken daily, at about the same time each day, for 28 consecutive days (one pink active tablet taken daily during the first 24 days, and one white inactive tablet taken daily during the following 4 days).

Previous PBAC consideration

- 2.6 E4/DRSP has not been previously considered by the PBAC.
- 2.7 At its July 2024 meeting, the PBAC recommended listing drospirenone 3 mg with ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 3 x 28 (Yaz[®]) and drospirenone 3 mg with ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 3 x 28 (Yasmin[®]), as Unrestricted Benefit listings, on a cost-minimisation basis with levonorgestrel 150 micrograms with ethinylestradiol 20 micrograms combination tablets. At its November 2024 meeting the PBAC provided further advice to its July 2024 recommendation with regards to its recommended price (see paragraph 2.12).
- 2.8 In a separate consideration at its November 2024 PBAC meeting, the PBAC recommended listing the oral contraceptive pill drospirenone 4 mg tablets on the PBS at a price consistent with the price recommended for other newer oral contraceptive pills.

¹ Australian Government Department of Health, (2018), ‘National Women’s Health Strategy 2020-2030’, Canberra. Available at: www.health.gov.au/resources/publications/national-womens-health-strategy-2020-2030?language=en

Current PBS listings for combined oral contraceptives

- 2.9 The following COCs are currently listed on the PBS as Unrestricted Benefit listings:
- levonorgestrel 100 microgram + ethinylestradiol 20 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Femme-Tab[®] ED 20/100)
 - levonorgestrel 125 microgram + ethinylestradiol 50 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Microgynon[®] 50 ED)
 - levonorgestrel 150 microgram + ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Eleanor 150/30 ED, Evelyn 150/30 ED, Femme-Tab 30/150 ED, Leveth 150/30 ED, Lenest[®] 30 ED, Micronelle[®] 30 ED, Levlen[®] ED)
 - levonorgestrel 50 microgram + ethinylestradiol 30 microgram tablet [6] (& levonorgestrel 75 microgram + ethinylestradiol 40 microgram tablet [5] (& levonorgestrel 125 microgram + ethinylestradiol 30 microgram tablet [10] (& inert substance tablet [7], 4 x 28 (Logynon[®] ED, Trifeme[®] 28, Triquilar[®] ED)
 - norethisterone 1 mg + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Norimin-1 28 Day)
 - norethisterone 500 microgram + ethinylestradiol 35 microgram tablet [21] (& inert substance tablet [7], 4 x 28 (Norimin 28 Day).
- 2.10 In October 2024, at the request of the Minister for Health and Aged Care, the PBAC convened a stakeholder meeting to discuss evidence available that may demonstrate additional benefits of newer oral contraceptives compared to older generation oral contraceptives. Invited participants included those representing professional organisations, pharmaceutical companies responsible for newer contraceptives, clinicians with expertise in women’s health, members of the PBAC and Department representatives.
- 2.11 It was noted at the stakeholder meeting that it was important to have a range of hormonal contraceptive options available on the PBS as choice of therapy can be highly individualised, and in certain clinical situations newer oral contraceptive pills (OCPs) are more appropriate compared to OCPs currently PBS-listed. Stakeholders also commented that there are equity and access issues with newer OCPs not being available on the PBS, due to the private price of these medicines and subsequent affordability.
- 2.12 At the July 2024 meeting, the PBAC recommended listing drospirenone 3 mg with ethinylestradiol 20 microgram tablet [24] (& inert substance tablet [4], 3 x 28 (Yaz[®]) and drospirenone 3 mg with ethinylestradiol 30 microgram tablet [21] (& inert substance tablet [7], 3 x 28 (Yasmin[®]), as Unrestricted Benefit listings, on a cost-minimisation basis with levonorgestrel 150 micrograms with ethinylestradiol 20 micrograms combination tablets. At its November 2024 meeting, the PBAC provided further advice regarding the July 2024 recommendation after the sponsor

requested the PBAC reconsider its cost-minimisation recommendation. The PBAC considered Yaz and Yasmin may provide a different option for some people than the currently PBS-listed COCs and that it was important to have a range of COC options on the PBS. The PBAC considered that Yaz and Yasmin offer benefits in certain clinical situations compared to other COCs and accepted the sponsor’s proposed price. Yaz and Yasmin were listed on the PBS on 1 March 2025.

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

3 Requested listing

3.1 The submission requested the following new listing. Suggested deletions proposed by the Secretariat are crossed out in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTETROL + DROSPIRENONE					
Estetrol 14.2 mg + drospirenone 3 mg tablet [24] (& inert substance tablet [4], 3 x 28	NEW	1	3	3	Nextstellis
Restriction Summary / Treatment of Concept:					
	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				
	Restriction type: <input checked="" type="checkbox"/> Unrestricted benefit				
	Indication: Contraception				

3.2 The submission requested a General Schedule Unrestricted Benefit listing for E4/DRSP, consistent with other COCs listed on the PBS. The requested listing specified that the indication would be for contraception. This is not consistent with an unrestricted listing where access through the PBS is not dependent on indication.

3.3 The submission requested that medical practitioners and nurse practitioners be included as eligible prescribers for E4/DRSP, consistent with other COCs listed on the PBS.

3.4 The requested listing included a maximum quantity of 84 tablets (3 x 28) and a maximum of 3 repeats. The requested maximum quantity and number of repeats is sufficient for approximately 12 months of treatment when used at the recommended dose of 1 tablet daily, consistent with other PBS-listed COCs.

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. The choice of contraception is most often determined by individuals on a personal choice basis and discussion with a health care professional. Contraception options in Australia include oral contraceptives,

intrauterine devices, long-acting reversible contraceptives (LARCs), the emergency contraceptive pill, vaginal ring, surgical methods and other non-medical methods including condoms, fertility tracking and withdrawal. Oral contraceptives are used by between 27% to 34%^{2,3,4} of Australian women, as cited by the submission, and includes progestogen-only pills (POP) and COCs, which are available as fixed combinations or sequential preparations of progestogens and estrogens. An alternative reference cited a 2015 survey which found that oral contraception was the most commonly used form of contraception, with 28% of women using this method.⁵ No sources that were nationally representative and more recent than the Skiba study were identified during the evaluation.

- 4.2 The Therapeutic Guidelines outline several factors that influence contraceptive choice, including: contraindications, precautions and adverse effects of the contraceptive; potential for drug interactions; effectiveness of the method and consequences of unintended pregnancy; need for an immediate start; reproductive stage of life; timeframe for planned pregnancies; mechanism of action (a method that prevents ovulation may be preferred); reversibility; non-contraceptive benefits (such as improved bleeding patterns); cost and accessibility.⁶
- 4.3 The Therapeutic Guidelines states a monophasic formulation containing ethinylestradiol (20 or 30 micrograms) and levonorgestrel is first line COC.⁷ However, it was noted at the PBAC Stakeholder meeting for oral contraceptives that not every individual responds the same way to oral contraceptives, and although some contraceptives are generally better tolerated than others, the choice of contraceptive is highly individualised based on the medicines that an individual may or may not

²Richters, J., Grulich, A.E., et al. (2003), 'Contraceptive practices among a representative sample of women', Australian and New Zealand Journal of Public Health, 27(2):pp.210-6.

³Australian Bureau of Statistics, (2001), 'National Health Survey' accessed 26 November 2024. Available at: [www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/90A3222FAD5E3563CA256C5D0001FD9D/\\$File/43640_2001.pdf](http://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/90A3222FAD5E3563CA256C5D0001FD9D/$File/43640_2001.pdf)

⁴Skiba, M.A., Islam, R.M., et al. (2019), 'Hormonal contraceptive use in Australian women: Who is using what?', Aust NZ Obstet Gynaecol, 59(5):pp.717-24.

⁵ Family planning NSW, (2018), 'Contraception in Australia 2005-2018', accessed 13 January 2025. Available at: <https://app-tg-org-au.ap1.proxy.openathens.net/viewTopic?etgAccess=true&guidelinePage=Sexual%20and%20Reproductive%20Health&topicfile=contraceptive-choice>

⁶Therapeutic Guidelines, (2023), 'Choice of contraceptive method', accessed 2 December 2024. Available at: <https://app-tg-org-au.ap1.proxy.openathens.net/viewTopic?etgAccess=true&guidelinePage=Sexual%20and%20Reproductive%20Health&topicfile=contraceptive-choice>

⁷Therapeutic Guidelines, (2023), 'Combined hormonal contraception', accessed 2 December 2024. Available at: <https://app-tg-org-au.ap1.proxy.openathens.net/viewTopic?etgAccess=true&guidelinePage=Sexual%20and%20Reproductive%20Health&topicfile=combined-hormonal-contraception>

tolerate.⁸ In addition, there are certain clinical situations where specific OCPs are more appropriate than others (paragraph 2.11).

- 4.4 The Therapeutic Guidelines state that estetrol, similar to estradiol and estradiol valerate, has less of an effect on laboratory markers for venous thromboembolism (VTE) and cardiovascular disease (CVD) compared to ethinylestradiol. However, it is also noted that further data is required to determine whether the risk of VTE and CVD is reduced.⁶
- 4.5 The Therapeutic Guidelines note that while evidence is lacking to guide the choice of COC based on the progestogen component, COCs containing drospirenone (along with cyproterone, desogestrel and gestodene) may have a slightly higher risk of VTE compared to those containing levonorgestrel or norethisterone.⁶
- 4.6 E4/DRSP is an oral fixed dose combination tablet containing estetrol, a synthetic analogue of a native human estrogen, and drospirenone, a synthetic progestational compound. Estetrol exhibits high selectivity for estrogen receptors (ER α and ER β) and acts as an estrogen agonist. Drospirenone possesses antigonadotrophic, antiandrogenic, and mild antimineralocorticoid properties and has no estrogenic, glucocorticoid, or antiglucocorticoid activity.

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

5 Comparator

- 5.1 The submission nominated any fixed dose COCs listed on the PBS at the time of the submission as the main comparator, including any listed combination of the estrogen, ethinylestradiol, combined with progestogens, levonorgestrel (hereafter EE/LNG) and norethisterone (hereafter EE/NETA) (see paragraph 2.9). The submission nominated combinations of ethinylestradiol with drospirenone (hereafter EE/DRSP), Yaz and Yasmin, as near market comparators.
- 5.2 While the submission nominated any fixed dose COCs as the comparator, inconsistencies were noted, as both sequential dose and fixed dose COCs were used in the economic and financial analysis. As the market share of sequential dose fixed dose COCs is small (approximately 4%), and the price is comparable to fixed dose COCs, the discrepancy in the economic and financial analysis were inconsequential.
- 5.3 Other hormonal contraceptives are listed on the PBS, including POPs (levonorgestrel 30 microgram tablet and norethisterone 350 microgram tablet), depot medroxyprogesterone injection, etonogestrel implant, and levonorgestrel intrauterine devices, and may be alternative therapies. Some of these alternative

⁸ Australian Government Department of Health and Aged Care, (2024), 'Oral Contraceptives Stakeholder Meeting Outcome Statement', accessed 14 January 2025. Available at: www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/Oral-Contraceptives-Stakeholder-Meeting-October-2024-Outcome-Statement.pdf

therapies are less costly than E4/DRSP. The ESC noted that a particular type of hormonal contraceptive may be preferred in certain clinical circumstances and that different hormonal contraceptives have different adverse effect profiles (e.g. COCs are contraindicated for some women, and adverse effects associated with depot medroxyprogesterone injection include loss of bone mineral density).

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 stated that estetrol is a newer natural estrogen, compared to the synthetic estrogen ethinylestradiol that is commonly used in other COCs. The clinician stated that E4/DRSP is well tolerated and provides a regular bleeding pattern. It has a good safety profile, with a similar bleeding profile to the COC EE/DRSP, and there was a low rate of discontinuations in studies due to adverse effects. The clinician stated that the estimated rate of VTE with E4/DRSP was 3.66/10,000 women years based on Phase 3 studies (and that these findings were being confirmed in future studies), and claimed this was a lower risk compared to using other COCs. The clinician stated that trials showed that E4/DRSP had good contraceptive efficacy in women with a higher BMI, and that while there was a slightly higher Pearl Index seen in women with a BMI of 30-35 kg/m² (2.9 versus 2.6 in women with a lower BMI), the Pearl Index still demonstrated acceptable contraceptive effectiveness in this patient group.

Consumer comments

- 6.2 The PBAC noted and welcomed input from individuals (1), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with E4/DRSP, including providing effective contraception and menstrual management (such as providing regular periods and controlling irregular bleeding), and a lower risk of causing hormonal and mental health side effects, leading to better quality of life. Input stated that E4/DRSP has a better safety profile compared to older oral contraceptive pills, which leads to better tolerance and compliance, and therefore lower risk of unplanned pregnancies. Input stated E4/DRSP has a reduced risk of causing VTE, although one comment stated that as this is a newer product, the scientific evidence is limited. Comments stated that E4/DRSP is beneficial for contraception in women who also have conditions such as polycystic ovarian syndrome. Input noted a desire for equity and access issues to be addressed, as the private price of this medicine is prohibitive for women to consider its use, and it is important that there are more affordable options available to women seeking reliable contraception.
- 6.3 The National Aboriginal Community Controlled Organisation (NACCHO) stated that where oral contraceptives are not listed on the PBS, for Aboriginal and Torres Strait

Islander peoples eligible for the Closing the Gap (CTG) PBS Co-payment program, there is a significant increase in cost to patients, which can lead to a greater risk of reduced adherence and subsequent unintended pregnancies. In remote areas where patients access medicines through the Remote Area Aboriginal Health Service S100 Scheme, not having E4/DRSP listed on the PBS creates barriers to access for these patients as they are unable to access it through this program.

- 6.4 NACCHO stated that estetrol may have a lower risk of VTE compared to alternative contraceptives listed on the PBS containing ethinylestradiol, however also noted that as this is a new medication the risk of VTE is unclear. Cardiovascular risk, including for Aboriginal and Torres Strait Islander peoples, should be taken into account when considering an appropriate contraceptive for an individual. NACCHO also commented on the anti-mineralocorticoid and anti-androgenic effects of drospirenone, and its potential benefits in reducing acne, as well as possible benefits on mood.

Clinical studies

- 6.5 The submission claimed that the efficacy and bleeding profile of E4/DRSP were established based on its approval by the TGA. The submission therefore relied on the TGA Clinical Evaluation Report to inform the contraceptive efficacy and short-term safety of E4/DRSP. In summary, the efficacy and short-term safety evidence was based on two Phase III, multicentre, open-label, single-arm studies: MIT-Es0001-C301 and MIT-Es0001-C302, and four supportive Phase II studies (ES-C01, ES-C02, MIT-Es0001-C201, and MIT-Es0001-C202). Apart from MIT-Es0001-C201, these studies were not presented in the submission as the focus of the submission was the long-term safety; however, the details of these studies were presented in Attachment 2 of the submission.
- 6.6 To inform long-term safety of E4/DRSP in terms of risks of VTE and CVD compared to the other COCs, the submission relied on data from a Phase II, randomised, single-centre, open-label, three-arm study (MIT-Es0001-C201), which compared E4/DRSP with EE/LNG (30 microgram/150 microgram) and EE/DRSP (20 microgram/3 mg) on a range of serum variables. Additionally, the submission included a supportive efficacy study (MIT-Es0001-C202), two Cochrane reviews (Roach et al., 2015 and de Bastos et al., 2014), one observational cohort study (Lidegaard et al., 2012), and a review paper (Morimont et al., 2021) to support the claim of superior safety. However, none of these supportive studies included E4/DRSP.
- 6.7 Overall, the literature search was satisfactory. An independent search located one potentially relevant study by Didembourg et al. (2024)⁹, a disproportionality analysis of the EudraVigilance database on the risk of VTE with E4/DRSP and other COCs. The

⁹ Didembourg M., Locquet M., Raskin L., et al., (2024), 'Lower reporting of venous thromboembolisms events with natural estrogen-based combined oral contraceptives compared to ethinylestradiol-containing pills: A disproportionality analysis of the Eudravilgiance database', *Contraception*, 17:110727.

EudraVigilance is a system developed by the European Medicines Agency (EMA) for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the European Economic Area. The analysis found that E4/DRSP exhibited the lowest proportionality reporting rate (0.12), which was similar to progestogen-only pills, while EE/DRSP had the highest proportionality reporting rate (2.25), indicating an increased thrombotic risk. The proportionality reporting rate for EE/LNG was found to be 0.47. The authors suggested that study results supported the safer thrombotic profile of natural estrogen-based COCs (i.e. E4), over synthetic EE. However, the authors conceded study limitations, which included potential under-reporting, reporting biases and the challenge of assessing outcomes in the absence of a defined population at risk.

- 6.8 The Pre-Sub-Committee Response (PSCR) claimed that the result of the Didembourg et al study provided support that E4/DRSP has the lowest risk of VTE compared to multiple contraceptive choices.
- 6.9 Details of the studies presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Pivotal data for the safety assessment in the main body submission		
	A single center, randomized, open-label, controlled, three-arm study to evaluate the effect of a new combined oral contraceptive (COC) containing 15 mg estetrol (E4) and 3 mg drospirenone (DRSP) and of two reference COCs containing either 30 mcg ethinylestradiol (EE) and 150 mcg levonorgestrel (LNG) or 20 mcg EE and 3 mg DRSP on endocrine function, metabolic control and hemostasis during 6 treatment cycles.	17 April 2019
MIT-Es0001-C201	Klipping C, Duijkers I, Mawet M, et al. Endocrine and metabolic effects of an oral contraceptive containing estetrol and drospirenone.	Contraception 2021; 103(4):213-21.
	Douxflis J, Klipping C, Duijkers I, et al. Evaluation of the effect of a new oral contraceptive containing estetrol and drospirenone on hemostasis parameters.	Contraception 2020; 102(6):396-402.
	Morimont L, Jost M, Gaspard U, et al. Low thrombin generation in users of a contraceptive containing estetrol and drospirenone.	J Clin Endocrinol Metab 2022; 108(1):135-43.
	A single-center, randomized, open-label, two-arm study to evaluate the ovarian function inhibition of a monophasic combined oral contraceptive (COC) containing 15 mg estetrol (E4) and 3 mg drospirenone (DRSP) and a monophasic COC containing 20 mcg ethinylestradiol (EE)/3 mg DRSP (Yaz®), administered orally once daily in a 24/4 day regimen for three consecutive cycles.	07 March 2019
MIT-Es0001-C202	Duijkers I, Klipping C, Kinet V, et al. Effects of an oral contraceptive containing estetrol and drospirenone on ovarian function.	Contraception 2021; 103(6):386-393.
Supplementary studies		
Cochrane systematic review	de Bastos M, Stegeman BH, Rosendaal FR, et al. Combined oral contraceptives: venous thrombosis.	Cochrane Database Syst Rev 2014; 2014(3):CD010813.
Cochrane systematic review	Roach RE, Helmerhorst FM, Lijfering WM, et al. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke.	Cochrane Database Syst Rev 2015;2015(8):CD011054.
Review paper	Morimont L, Haguet H, Dogné J, et al. Combined oral contraceptives and venous thromboembolism: Review and perspective to mitigate the risk.	Front Endocrinol (Lausanne) 2021; 12:769187.
Observational cohort study	Lidegaard Ø, Løkkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception.	N Engl J Med 2012; 366(24):2257-66.
Pivotal efficacy and safety data provided as attachment and references		
	A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone (E4 FREEDOM: Female Response concerning Efficacy and safety of Estetrol/Drospirenone as Oral contraceptive in a Multicentric study).	14 March 2019
MIT-Es0001-C301 E4 FREEDOM-1	Gemzell-Danielsson K, Apter D, Zatik J, et al. Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia.	BJOG 2022; 129(1):63-71.
	A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone (E4 FREEDOM: Female Response concerning Efficacy and safety of Estetrol/Drospirenone as Oral contraceptive in a Multicentric study).	17 April 2019
MIT-Es0001-C302 E4 FREEDOM-2		

Trial ID	Protocol title/ Publication title	Publication citation
	Creinin MD, Westhoff CL, Bouchard C, et al. Estetrol-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results.	Contraception 2021; 104(3): 222-8.
Pooled efficacy results	Integrated Summary of Effectiveness Estetrol monohydrate 15 mg/drospirenone 3 mg (E4/DRSP 15/3 mg).	05 Dec 2019
	Jensen JT, Kaunitz AM, Achilles SL, et al. Pooled efficacy results of estetrol/drospirenone combined oral contraception phase 3 trials.	Contraception 2022; 116:37-43.
Pooled safety analysis	Integrated Safety Summary of selected studies was performed to demonstrate the safety of E4/DRSP 15/3 mg for the therapeutic indication “oral contraception”.	31 March 2022
	Chen MJ, Jensen JT, Kaunitz AM, et al. Tolerability and safety of the estetrol/drospirenone combined oral contraceptive: Pooled analysis of two multicenter, open-label phase 3 trials.	Contraception 2022; 116:44-50.

Source: Table 2.2, p38-41 of the submission main body.

6.10 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
E4/DRSP versus EE/LNG and EE/DRSP					
MIT-Es0001-C201	98; E4/DRSP=38 EE/LNG=29 EE/DRSP=31	RCT, OL, P, SC Six cycles of 28-days	High ^{a*}	Healthy women aged 18 to 47 years with BMI between 18 and 30 kg/m ²	Primary endpoints: haemostatic parameters; endocrine parameters; liver proteins; lipid profile and glucose metabolism Secondary endpoints: adverse events; vital signs, physical and gynaecological examination, clinical laboratory, ECG, echocardiogram, MDQ

Source: Section 2.6.2.1, pp44-48; Section 2.6.2.4.1, pp50-51 of the submission main body; Douxfils et al. (2020)

BMI = body mass index; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; ECG = electrocardiogram; EE/LNG = ethinylestradiol 30 mcg/levonorgestrel 150 mcg; EE/DRSP = ethinylestradiol 20 mcg/drospirenone 3 mg; MDQ = Menstrual distress questionnaire Form C; N = total participants in group; OL = open label; P = parallel; RCT = randomised controlled trial; SC = single-centre.

^a Based on Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

*added during evaluation.

6.11 The MIT-Es0001-C201 study had a high risk of bias in four domains – selection, performance, detection, and attrition – due to the open-label design, with no evidence on allocation, testing and assessment concealment. Selective reporting cannot be ruled out, as the proportion of analysed population for haemostatic parameters varied across the three arms: 87% in E4/DRSP arm, 90% in EE/LNG, and 94% in EE/DRSP arm. Overall, the risk of bias in MIT-Es0001-C201 study was considered high.

6.12 The submission claimed that E4/DRSP is superior to both the PBS-listed and the near market COCs in terms of specific longer-term safety, including the risk of VTE and the risk of myocardial infarction (MI) and stroke. However, the submission presented MIT-Es0001-C201 which reported a range of serum variables (biomarkers), including haemostatic parameters; endocrine parameters; liver proteins; lipid profile; and glucose metabolism, as the surrogate markers that may be associated with the risk of

VTE and MI/stroke to support the safety of E4/DRSP. The MIT-Es0001-C201 did not measure any cardiovascular outcomes.

- 6.13 Additionally, the MIT-Es0001-C201 study partially complied with the requirements outlined below, as recommended by the EMA ‘Guideline on clinical investigation of steroid contraceptives in women’ (2005)¹⁰ for the development of hormonal contraceptives to address safety concerns and rare risks (e.g., cardiovascular events and VTE), which include:
- A minimum of 400 women should complete one year of treatment to provide adequate safety data.
 - Biomarker comparative studies should use a crossover design.
 - Serious adverse events (SAEs), such as cardiovascular events or VTE, should be carefully documented and analysed in relation to established predisposing risk factors in the study population.
- 6.14 Additionally, the Guideline recommends that if there is a reduction in the dose of steroid in an existing product, the new product should also be compared with the higher dose product.
- 6.15 Pertaining to the aforementioned EMA Guideline, the MIT-Es0001-C201 study included 98 women over a 6-cycle non-crossover biomarker comparative study of which SAEs were not documented. Also, comparisons were made with EE/LNG (30 mcg/150 mcg), which was appropriate as this was one of the recommended comparators in the Guideline. The other comparator used was EE/DRSP (20 microgram/3 mg); there is a COC with a higher dose of ethinylestradiol available (EE/DRSP 30 micrograms/3 mg), although both EE/DRSP combinations contain the same dose of DRSP as what is in E4/DRSP.
- 6.16 For E4/DRSP compared to EE/LNG and EE/DRSP, the approach used to estimate the risk of MI and stroke was based on: (a) changes in lipid profile and (b) variations in estrogen dose across the COCs. The approach used to estimate the risk of VTE was based on: (a) VTE events in the pooled studies of E4/DRSP compared to EMA surveillance data for EE/LNG and EE/DRSP, (b) changes in sex hormone binding globulin (SHBG) as a proxy for estrogenicity, and (c) changes in normalised activated protein C sensitivity resistance (nAPCsr).
- 6.17 The aforementioned EMA Guideline states that there are no generally accepted surrogate endpoints for risk of cardiovascular events or VTE; however, the biological variables which may reflect different pharmacological effects, possibly related to VTE,

¹⁰ European Medicines Agency (EMA), (2005), ‘Guideline on clinical investigation of steroid contraceptives in women’, accessed 1st August 2024. Available at: www.tga.gov.au/sites/default/files/2024-06/guideline-clinical-investigation-steroid-contraceptives-women-ema.pdf

should be investigated when developing an estrogen/progestogen contraceptive.¹⁰ Variables suggesting such different pharmacological effects can include prothrombin fragment 1+2, activated protein C (APC) resistance (endogenous thrombin potential [ETP]-based, activated partial thromboplastin time [APTT]-based), d-dimer, factor VII, factor VIII, factor II, antithrombin, protein S, protein C and SHBG.¹⁰ Furthermore, published literature indicates that the APC pathway is a well-documented surrogate biomarker of estrogen-related VTE risk in both combined hormonal contraceptive users and non-users. Additionally, SHBG levels are associated with VTE risk.¹¹

- 6.18 Generally, the study population for MIT-Es0001-C201 was representative of the Australian population, noting that the body mass index (BMI) in the study population was 18-30 kg/m², whereas approximately 31% of the women in Australia reported a BMI >30 kg/m².¹² The ESC noted there is limited evidence as to whether individuals with a BMI >30 kg/m² using a COC have a higher risk of VTE compared to individuals with a lower BMI¹³, and that the use of COCs in individuals with a BMI ≥30 kg/m² is medical eligibility criteria for contraceptive use (MEC) criteria 2 (a condition where the advantages of using this method generally outweigh the theoretical or proven risks).¹⁴

Comparative effectiveness

Contraceptive efficacy

- 6.19 The submission did not provide an assessment of the contraceptive efficacy of E4/DRSP. The TGA Clinical Evaluation Report and other relevant documentation were provided as attachments to the submission.
- 6.20 Based on the TGA Clinical Evaluation Report (2020), E4/DRSP demonstrated good contraceptive efficacy with a Pearl Index of 1.52 (95% Confidence interval [CI]: 1.03, 2.16) among 2,837 subjects aged 16 to 35 years who provided 26,455 at-risk cycles, as evaluated in the pooled MIT-Es0001-C301 and MIT-Es0001-302 studies. The difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the Pearl Index (point estimate) does not exceed 1 (2.16-1.52 = 0.64) and fulfils the criterion on the precision of the estimate according to the EMA 'Guideline on clinical investigation of steroid contraceptive' (2005).¹⁰ However, the results were not consistent across both studies with significant results only observed in the

¹¹ Hugon-Rodin, J., Fontana, P., et al., (2024), 'Longitudinal profile of estrogen-related thrombotic biomarkers after cessation of combined hormonal contraceptives.', *Blood*, 143 (1):pp.70–78.

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 Faculty of Sexual & Reproductive Healthcare, (2019), 'Overweight, obesity and contraception', UK: Faculty of Sexual & Reproductive Healthcare. Available at: https://srh.bmj.com/content/familyplanning/45/Suppl_2/local/front-matter.pdf

¹⁴ World Health Organization, (2015), 'Medical eligibility criteria for contraceptive use, Fifth edition', Geneva: World Health Organization. Available at: www.who.int/publications/i/item/9789241549158

European/Russian study C301 while the pivotal North American study C302 showed a higher Pearl Index which did not fulfill the criterion on the precision of the estimate.

- 6.21 Subgroup analysis for the primary efficacy endpoint (Pearl Index in women aged 16-35 years) showed a tendency for reduced contraceptive efficacy (higher Pearl Index) in women who had higher BMI (>30 kg/m²), had no prior COC use (starters) and were current smokers. In Australia, approximately 31% women are obese¹², with a BMI >30 kg/m², which could potentially impact the contraceptive efficacy of E4/DRSP.

Comparative harms

Short-term safety

- 6.22 The submission did not examine the short-term safety profile of E4/DRSP. However, it stated that the short-term safety of E4/DRSP is covered in the TGA Clinical Evaluation Report, which was included as an appendix to the submission.
- 6.23 Based on the TGA Clinical Evaluation Report (2020), it was estimated that 1,924 (50.8%) women had at least one treatment-emergent adverse events (TEAEs). The most common TEAEs with E4/DRSP were headache (6.4%), metrorrhagia (4.6%), viral upper respiratory tract infection (3.9%), acne (3.7%), dysmenorrhea (3.3%), vaginal haemorrhage (3.1%), nausea (2.7%), urinary tract infection (2.5%), weight increased (2.6%), breast pain (2.3%) and abdominal pain (2.1%). A total of 45 serious adverse events (SAE) were reported by 41 subjects (1.1%) in the pooled Phase III (MIT-Es0001-C301 and MIT-Es0001-C302) and Phase II studies (ES-C01, ES-C02, MIT-Es0001-C201, and MIT-Es0001-C202). Three SAEs were considered related to study treatment (VTE, worsening depression and ectopic pregnancy).

Long-term safety for VTE, MI and stroke (based on biomarkers)

- 6.24 The submission included a range of haemostasis parameters, endocrine markers, liver proteins, lipid profile, and glucose levels as surrogate markers for the safety of E4/DRSP over EE/LNG and EE/DRSP. However, only the parameters pertinent to the claim are discussed here.
- 6.25 The median values at baseline and at cycle 6, as well as the median percentage change from baseline of the different treatment arms on the key parameters is summarised in Table 4.

Table 4: Results of key biomarkers in MIT-Es0001-C201 study

Parameter	Treatment	Baseline, median (min, max)	Value at cycle-6, median (min, max)	Changes from baseline, %
Haemostasis parameters				
APC resistance, ETP-based, nAPCsr	E4/DRSP	1.7 (0.5,3.4)	2.1 (0.8,4.3)	30.0*
	EE/LNG	1.5 (0.0,5.0)	3.4 (0.7,7.4)	164.5*
	EE/DRSP	1.4 (0.5,3.1)	4.5 (2.5,5.9)	218.5*
D-dimer, mcg/mL FEU	E4/DRSP	0.3 (0.3,0.4)	0.3 (0.3,0.6)	4.0*
	EE/LNG	0.3 (0.3,2.3)	0.3 (0.3,1.2)	7.0
	EE/DRSP	0.3 (0.3,1.1)	0.3 (0.3,0.9)	0.0
SHBG, nmol/L	E4/DRSP	64.8 (25.3,117.9)	87.2 (52.7,196.0)	55.0*
	EE/LNG	67.3 (27.1,144.4)	119.8 (65.2,191.4)	74.0*
	EE/DRSP	70.6 (36.2,125.6)	264.3 (162.3,447.4)	251.0*
Lipid profile				
Triglycerides, mg/dL	E4/DRSP	71.5 (36,125)	77.5 (50,228)	24.0*
	EE/LNG	65.0 (32,134)	88.0 (34,227)	28.0*
	EE/DRSP	62.5 (36,138)	103.0 (63,238)	65.5*
LDL-C, mg/dL	E4/DRSP	89.5 (35,145)	89.0 (41,146)	-2.0
	EE/LNG	89.0 (43,163)	98.0 (49,146)	7.0
	EE/DRSP	92.0 (28,149)	85.5 (23,144)	-5.0
HDL-C, mg/dL	E4/DRSP	66.0 (43,93)	66.0 (52,91)	4.0
	EE/LNG	69.0 (45,89)	59.0 (37,74)	-16.0*
	EE/DRSP	68.5 (44,102)	76.0 (49,107)	8.5*
Apolipoprotein A1 ^a , mg/dL	E4/DRSP	161.0 (125,217)	174.5 (133,220)	5.0*
	EE/LNG	164.0 (123,202)	160.0 (120,194)	-3.0*
	EE/DRSP	162.0 (114,227)	190.5 (140,264)	19.5**
Apolipoprotein B ^b , mg/dL	E4/DRSP	73.5 (31,120)	79.0 (35,139)	4.0*
	EE/LNG	73.0 (36,140)	90.0 (45,132)	23.0*
	EE/DRSP	72.0 (28,104)	80.0 (31,135)	11.5*
Endocrine parameters				
FSH (mIU/mL)	E4/DRSP	4.5 (1.6,13.0)	4.6 (0.5,9.6)	30.5
	EE/LNG	4.5 (1.8,24.1)	1.0 (0.1,4.2)	-84.0*
	EE/DRSP	5.1 (1.6,14.3)	0.7 (0.1,7.8)	-64.0*
LH (mIU/mL)	E4/DRSP	7.3 (1.3,36.3)	6.1 (0.2,13.0)	-7.5
	EE/LNG	8.4 (2.8,136.7)	0.7 (0.1,6.8)	-92.0*
	EE/DRSP	9.4 (1.7,75.2)	0.6 (0.1,8.4)	-90.0*
E2 (pg/mL)	E4/DRSP	113.5 (31.0,346.0)	13.5 (12.0,66.0)	-86.5*
	EE/LNG	148.0 (48.0,516.0)	12.0 (12.0,28.0)	-92.0*
	EE/DRSP	114.5 (23.0,579.0)	12.0 (12.0,82.0)	-87.0*
Cortisol (mcg/dL)	E4/DRSP	16.5 (9.6,25.9)	20.6 (11.2,32.7)	26.0*
	EE/LNG	15.2 (9.8,23.5)	32.7 (20.7,39.6)	109.0*
	EE/DRSP	17.7 (8.8,23.2)	37.7 (22.3,62.7)	107.0*

Source: Table 2.9, p53; Table 2.11, pp55-56; and Table 2.15, p60 of the submission main body.

APC = activated protein C; E2 = estradiol; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; EE/LNG = ethinylestradiol 30 mcg/levonorgestrel 150 mcg; EE/DRSP = ethinylestradiol 20 mcg/drospirenone 3 mg; ETP = endogenous thrombin potential; FEU = fibrinogen equivalent units; FSH = follicle stimulating hormone; HDL-C = high-density lipoprotein cholesterol; LH = luteinising hormone; LDL-C = low-density lipoprotein cholesterol; nAPCsr = normalised activated protein C sensitivity ratio; SHBG = sex hormone binding globulin.

^a Apolipoprotein A1 is the primary protein component of HDL.

^b Apolipoprotein B is the primary protein component of LDL.

* statistically significant results vs baseline, p<0.05 using a signed rank test.

Bold indicates statistically significant results vs E4/DRSP, p<0.05 using the Dwass-Steel-Critchlow-Fligner test.

6.26 The changes in biomarkers from baseline with the three COCs in the MIT-Es0001-C201 study after six treatment cycles are summarised as follows:

- Haemostatic parameters:
 - A statistically significant increase in the ETP-based on nAPCsr was observed from baseline with all three COCs. Notably, both EE/LNG (+165%) and EE/DRSP (+219%) showed statistically significant increases compared to E4/DRSP (+30%).
 - A statistically significant increase in the SHBG levels was observed from baseline with all three COCs. The increase was statistically significant with EE/DRSP (+251%) but not with EE/LNG (+74%), compared to E4/DRSP (+55%).
 - A statistically significant increase in the D-dimer level was observed with E4/DRSP from baseline but not with EE/LNG and EE/DRSP. No statistically significant difference was observed in EE/LNG (+7%) and EE/DRSP (+0%) compared to E4/DRSP (+4%).
- Endocrine parameters:
 - Follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels decreased statistically significantly with EE/LNG and EE/DRSP, but not with E4/DRSP. Both EE/LNG (-84% and -92%, respectively) and EE/DRSP (-64% and -90%, respectively) showed statistically significant decreases in FSH and LH compared to E4/DRSP (+31% and -8%, respectively).
 - A statistically significant change in the estradiol (E2) and cortisol levels was observed from baseline with all three COCs. Both EE/LNG (+109%) and EE/DRSP (+107%) showed statistically significant increases in cortisol levels compared to E4/DRSP (+26%).
- Lipid profile:
 - Triglyceride levels statistically significantly increased from baseline with all three COCs. The increase was statistically significant with the EE/DRSP arm (+66%) but not with EE/LNG (+28%), compared to the E4/DRSP arm (+24%). The ESC noted that while triglyceride levels increased, they were still within the normal reference interval.
 - No significant changes from baseline were observed in the low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels with E4/DRSP (-2% and +4% respectively). In contrast, while no significant change in the LDL-C levels was observed with EE/LNG (+7%) and EE/DRSP (-5%), statistically significant change was noted for HDL-C with EE/LNG (-16%), compared to E4/DRSP.
- Liver protein:
 - The liver parameters, including C-reactive protein, cortisol binding globulin, thyroxin binding globulin, and angiotensinogen increased statistically

significantly from baseline for all COCs, except for C-reactive protein with EE/LNG.

- Glucose metabolism:
 - Carbohydrate parameters, including fasting insulin and glucose, C-peptide and haemoglobin A1c (HbA1c), remained relatively stable in all three COCs.

Risk of myocardial infarction and stroke

- 6.27 Based on the Cochrane review by Roach et al. (2015), the overall risk of MI or stroke was 1.6 times higher in women using a COC compared to non-users. When the analysis was stratified according to the estrogen dose, the risk of MI or stroke seemed to increase with higher doses of estrogen. E4/DRSP was not included in Roach et al. (2015) as it was not available at that time, with initial regulatory approvals by Health Canada, the EMA and United States Food and Drug Administration (FDA) granted only in 2021.
- 6.28 Lidegaard et al. (2012) analysed a large Danish database to assess the risks of MI and stroke associated with various hormonal contraceptives by estrogen dose, progestin type, and route of administration. Among 1,626,158 women contributing 14,251,063 person-years, the study recorded 3,311 thrombotic strokes (21.4 per 100,000 person-years) and 1,725 MI (10.1 per 100,000 person-years).
- 6.29 The submission estimated the combined risk for MI or stroke using data from Lidegaard et al. (2012) to align with the study by Roach et al. (2015), as presented in Table 5.

Table 5: Risk of myocardial infarction and ischaemic stroke

Population	Relative risk of MI/stroke*	Incidence rate, events per 10,000 patient years ^a	Impact on lipid profile ^b
COC non-users	1.0	2.42 ^e	-
E4 15 mg	1.2 ^c	NA	No changes except for increase in TG, Apo-A1 and Apo-B from baseline with E4/DRSP
EE 20 mcg	1.6 ^d	2.00	HDL-C, cholesterol, ratio HDL-C/LDL-C, Apo-A1, Apo-B and TG increased from baseline with EE/DRSP
EE 30-49 mcg	2.0 ^d	3.35	HDL-C and Apo-A1 decreased from baseline. Apo-B and TG increased from baseline with EE/LNG
EE > 49 mcg	2.4 ^d	9.01	Not evaluated in MIT-Es0001-C201 trial*

Source: Table 2.15, p60; Table 2.17, p65; Table 2.18, p68; and Section 2.7.1, p66 of the submission main body.

Apo-A1 = Apolipoprotein A1; Apo-B = Apolipoprotein B; COC = combined oral contraceptive; E4 = estetrol; EE = ethinylestradiol; E4/DRSP = estetrol 15 mg/ drospirenone 3 mg; EE/LNG = ethinylestradiol 30 mcg/ levonorgestrel 150 mcg; EE/DRSP = ethinylestradiol 20 mcg/drospirenone 3 mg; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides

^a estimates derived from data in Lidegaard et al., 2012

^b changes from baseline, based on MIT-Es0001-C201 trial

^c estimated by the submission by mapping the risks of MI/stroke reported in Roach et al. (2015) to the corresponding estrogen doses.

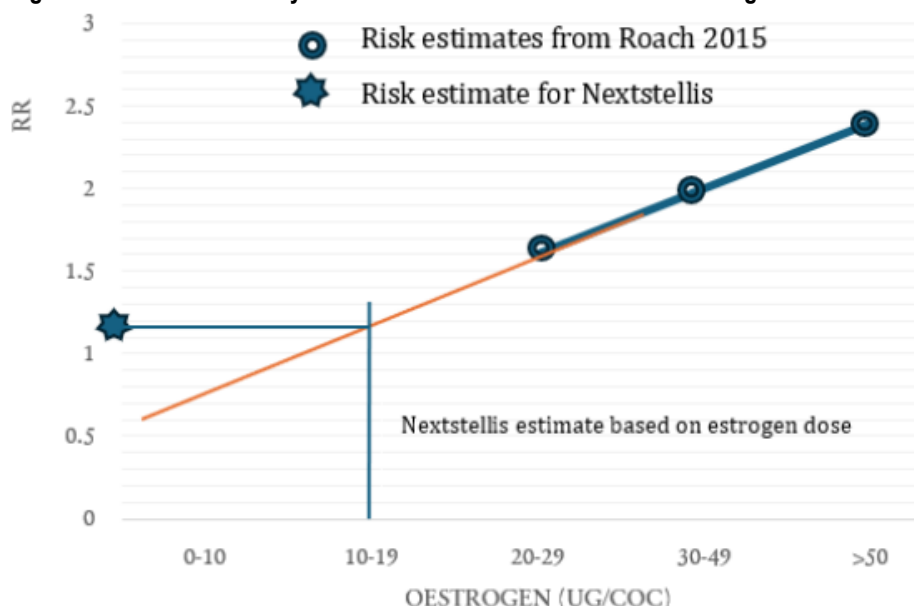
^d Relative risk of MI/stroke obtained from Cochrane review by Roach et al. (2015)

^e This was based on only the incidence rate of thrombotic stroke for COC non-users in the Lidegaard et al. (2012) study and not the combined incidence rate for MI and stroke.

*added during evaluation.

6.30 The submission stated that no cases of MI or stroke were reported in any of the trials of E4/DRSP. As presented in Figure 1, using the data from Roach et al. (2015), the submission mapped the risks of MI or stroke to corresponding estrogen doses and estimated the risk for E4/DRSP to be approximately 1.2, based on its estrogen dose.

Figure 1: Relative risk of myocardial infarction and stroke versus estrogen dose in microgram.



Source: Figure 2.4, p66 of the submission main body.

COC = combined oral contraceptive; RR = relative risk; UG = microgram.

Note: The risk of myocardial infarction or stroke was 1.6 with a contraceptive containing 20 micrograms of estrogen. The risk was 2.0 for 30-49 micrograms of estrogen. The risk was 2.4 for ≥ 50 micrograms of estrogen (Roach et al., 2015).

6.31 This mapping approach is highly uncertain, as it assumes a linear relationship between the dose of EE and the risk of MI and stroke, which lacks supporting evidence. Furthermore, the estrogen dose and type in E4/DRSP differs from those in the comparator COCs (i.e., EE), and the mapping of 15 mg E4 to 20 microgram EE was unjustified and unsupported by any equivalency study.

6.32 Additionally, the submission stated that E4/DRSP demonstrated the smallest changes from baseline in lipid parameters compared to EE/LNG and EE/DRSP, based on the MIT-Es0001-C201 study, and claimed this indicated the lowest impact on cardiovascular risk. Although variations were observed in lipid parameters at cycle 6 compared to baseline with EE/LNG and EE/DRSP, the values remained within the normal ranges (The Royal College of Pathologists of Australia manual¹⁵ stated that the reference intervals for triglycerides was <177 mg/dL; apolipoprotein A1 was >115 mg/dL; and for apolipoprotein B was <100 mg/dL).

¹⁵ The Royal College of Pathologists of Australasia, (2024), 'Triglycerides', accessed 27 November 2024. Available at: www.rcpa.edu.au/Manuals/RCPA-Manual/Pathology-Tests/T/Triglyceride

Risk of venous thromboembolism

- 6.33 As stated in paragraph 6.15, the VTE risk of COCs were based on: (a) VTE events in all the pooled studies of E4/DRSP and surveillance data for EE/LNG and EE/DRSP, (b) changes in SHBG as a proxy for estrogenicity, and (c) changes in nAPCsr.

Based on the available clinical trials or surveillance studies:

- 6.34 For E4/DRSP, the incidence of VTE observed in the pooled clinical studies (Phase III [MIT-Es0001-C301 and MIT-Es0001-C302] and Phase II studies [ES-C01, ES-C02, MIT-Es0001-C201, and MIT-Es0001-C202], based on one VTE event, was 2.80 per 10,000 women and the incidence rate based on 2,735 women-years (WY) exposure was 3.66 per 10,000 WY, as reported in the TGA Clinical Evaluation Report for E4/DRSP.
- 6.35 For COCs containing EE/LNG, EE/NETA, and EE with norgestimate, the risk of VTE was estimated at five to seven per 10,000 WY, while for COCs containing EE/DRSP, EE with desogestrel, and EE with gestodene, the risk was estimated at nine to 12 per 10,000 WY, based on the EMA Assessment report for combined hormonal contraceptives containing medicinal products¹⁶, as reported by Morimont et al. (2021). For comparison, the risk of VTE among non-pregnant non-users was estimated to be two per 10,000 WY.
- 6.36 There are two large ongoing post authorisation safety studies (PASS studies) for E4/DRSP: NCT06186271 (commenced in October 2024), and NCT06028555 (in the recruitment stage).
- 6.37 The TGA noted the estimated VTE risk of 3.66 per 10,000 WY with E4/DRSP, but considered the available clinical safety database to be too small to draw conclusions regarding the magnitude of VTE risk. Also, the Australian Public Assessment Report for E4/DRSP stated that the two events of VTE observed were considered to be related to treatment with E4/DRSP. The TGA further stated that E4/DRSP resulted in the least apparent changes from baseline for haemostatic parameters compared to EE/LNG and EE/DRSP which was considered to be reassuring; however, the clinical significance of the effects on haemostatic parameters with regard to risk of VTE is hypothetical. The TGA considered that the association between laboratory results (biomarkers) and VTE risk was weak and concluded that no claims regarding the relative risk for VTE with E4/DRSP in comparison with other COCs could be made based on the currently available data.

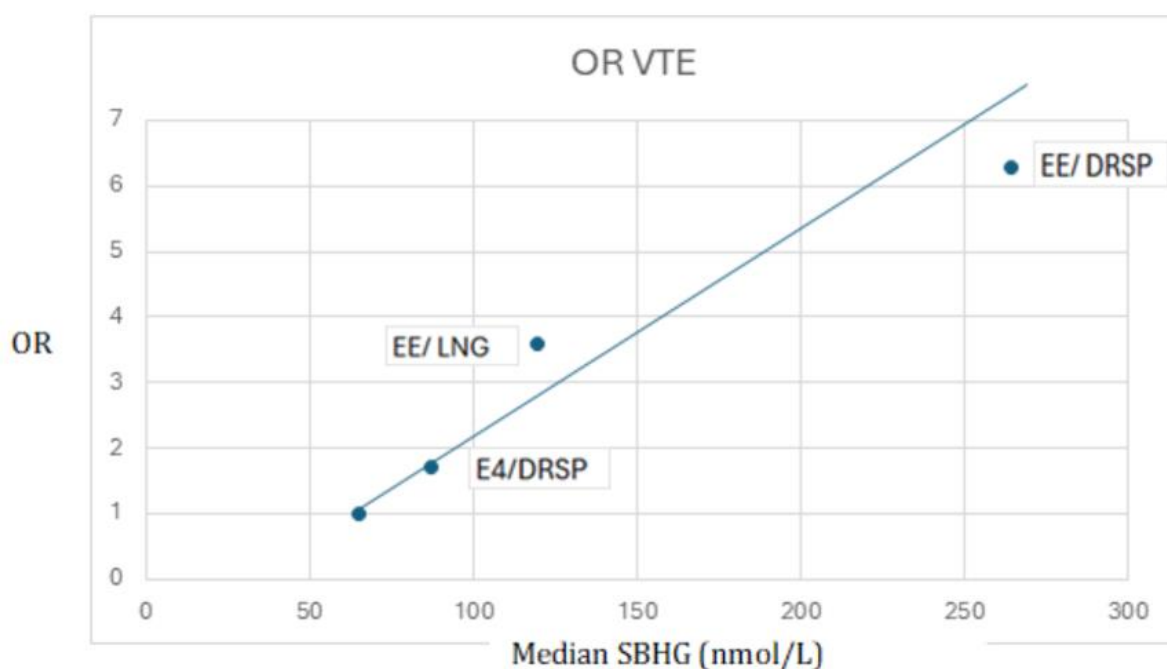
¹⁶ European Medicines Agency, (2014), 'Assessment report for combined hormonal contraceptives containing medicinal products', accessed 22 November 2024. Available at: www.ema.europa.eu/en/documents/referral/combined-hormonal-contraceptives-article-31-referral-prac-assessment-report_en.pdf

Based on changes in SHBG as a proxy for estrogenicity:

- 6.38 The submission stated that excessive estrogenicity, the sum of both the estrogen and progesterone contribution, was reported to increase the risk of VTE, and the SHBG biomarker best reflects the estrogenicity. Consequently, the median SHBG values obtained from the MIT-Es0001-C201 study were mapped to the odds ratios (OR) for the risk of VTE and SHBG levels of hormonal contraceptives reported by Raps et al. (2012)¹⁷, to estimate the risk of VTE for E4/DRSP. Raps et al. (2012) reported an odds ratio of 3.6 for EE/LNG and 6.3 for EE/DRSP.
- 6.39 As presented in Figure 2, the submission estimated that the changes in SHBG level induced by E4/DRSP (87 nmol/L) corresponded to a VTE OR of 1.7 compared to non-users (baseline SHBG of 65 nmol/L and OR of 1). The PSCR provided a revised Figure 2, stating that this revised figure changes the numerical values of the estimated OR for E4/DRSP derived from SHBG to 1.7 (1.4 in the submission), however stated the text regarding the estimate has not been altered in the legend and claimed the interpretation remains unchanged.

¹⁷ Raps, M., Helmerhorst, F., et al. (2012), 'Sex hormone-binding globulin as a marker for the thrombotic risk of hormonal contraceptives', *J Thromb Haemost*, 10(6):pp.992–997.

Figure 2: Revised odds ratio of venous thrombotic events (y-axis) vs median sex hormone binding globulin (SHBG) levels (x-axis) by contraceptive type^{b,c}



Source: Figure 2.9, p74 of the submission main body and p2 of the PSCR.

E4/DRSP = estetrol 15 mg/drospirenone 3 mg; EE/DRSP = ethinylestradiol 20 mcg/drospirenone 3 mg; EE/LNG = ethinylestradiol 30 mcg/levonorgestrel 150 mcg; OR = odds ratio; SHBG = sex hormone binding globulin; VTE = venous thromboembolism

^a An assumption of baseline SHBG level of 64.8 nmol/L (as reported in MIT-Es0001-C201 trial) corresponded to OR=1 for the risk of VTE.

^b EE/LNG: Ethinylestradiol/levonorgestrel (30 mcg/150 mcg) reported a SHBG level of 119.8 nmol/L in the MIT-Es0001-C201 trial.

^c EE/DRSP: Ethinylestradiol/drospirenone (20 mcg/3 mg) reported a SHBG level of 264.3 nmol/L in the MIT-Es0001-C201 trial.

Note: The corresponding ORs for the contraceptives were not traceable from Raps et al (2015).

*Added during evaluation

6.40 There were various uncertainties in the estimates presented by the submission:

- No direct evidence was presented to demonstrate association between the SHBG level and risk of VTE for E4/DRSP.
- The OR for EE/LNG and EE/DRSP in Figure 2 did not match the OR values reported by Raps et al. (2012). Furthermore, the methodology used to estimate the OR for VTE based on SHBG levels was not clearly outlined or traceable in the submission.
- Raps et al. (2012), an observational study, obtained mean SHBG levels from 262 contraceptive users and correlated these levels with the VTE risk associated with COCs from different studies.
- The magnitude of risk reduction was uncertain due to the approach adopted by the submission to estimate the risk of VTE with E4/DRSP compared to other COCs.

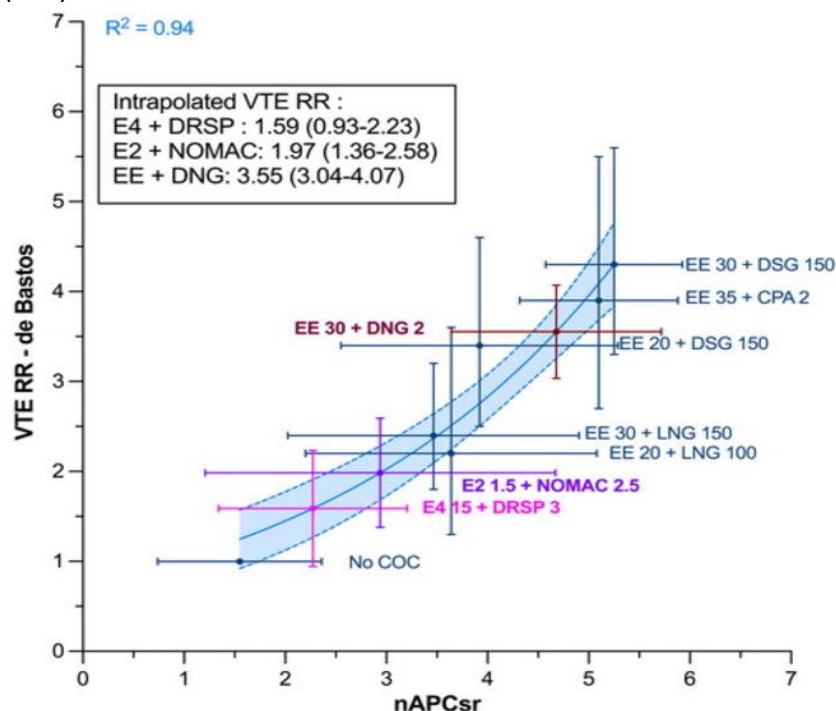
Based on changes in nAPCs:

6.41 The submission proposed using nAPCs to predict the risk of VTE, and stated that activated protein C resistance, measured with an ETP-based assay, has been a suitable marker for assessing the thrombogenicity of COCs for two decades. It cited Morimont

et al. (2021) and Raps et al. (2012) to support this claim. In 2005 the Committee for Medicinal Products for Human Use of the EMA considered that APC resistance should be studied when new steroid contraceptives are developed. However, variable results between studies have occurred and there has been a lack of standardisation in the method used (Morimont et al. (2021)). Raps et al. (2012) measured the SHBG levels and nAPCsr values of different combination hormonal contraceptives, and compared SHBG levels with the risk of VTE found with the use of the combination hormonal contraceptives as reported in other literature.

- 6.42 The submission presented a mathematical modelling from Gemzell-Danielsson et al. (2022) which showed the correlation between the nAPCsr and the relative risk of VTE as observed in the Cochrane meta-analysis of de Bastos et al. (2014). Based on the model, as presented in Figure 3, the submission reported a relative risk (RR) of 1.6 for E4/DRSP, 2.3 for EE/LNG, and 3.9 for EE/DRSP (assuming the RR for EE/DRSP is similar to EE with cyproterone acetate as stated by de Bastos et al. (2014)).

Figure 3: nAPCsr computed against the relative risk of VTE as extracted from the publication of de Bastos et al. (2014).



Source: Figure 2.10, p77 of the submission main body.

COC = combined oral contraceptive; CPA = cyproterone acetate; DNG = dienogest; DRSP = drospirenone; DSG = desogestrel; E2 = estradiol; E4 = estetrol; EE = ethinylestradiol; LNG = levonorgestrel; nAPCsr = normalised activated protein C sensitivity ratio; NOMAC = nomegestrol acetate; VTE = venous thromboembolism; RR = relative risk.

Note: Based on this mathematical model, the relative risk of combined oral contraceptives not included in the initial meta-analysis has been interpolated, i.e. EE/DNG, E2/NOMAC and E4/DRSP. For EE/DNG and E2/NOMAC, the interpolated relative risk corresponds to the adjusted relative risk observed in the meta-analysis of Dinger et al. (2016)¹⁸ and in the PRO-E2 study for E2/NOMAC by Reed et al. (2021)¹⁹. Text in pink/red/purple suggests the RRs were interpolated.

6.43 There were various uncertainties in the estimates presented by the submission:

- No direct evidence was presented to demonstrate association between the nAPCsr level and risk of VTE for E4/DRSP.
- The source of the nAPCsr values used in the model was untraceable and did not align with the nAPCsr values observed in the MIT-Es0001-C201 study.
- The magnitude of risk reduction was uncertain due to the approach adopted by the submission to estimate the risk of VTE with E4/DRSP compared to other COCs.

6.44 The risk of VTE based on different sources, detailed above, for COCs is summarised in the Table 6 .

¹⁸ Dinger, J., Do Minh, T., et al., (2016), 'Impact of estrogen type on cardiovascular safety of combined oral contraceptives,' Contraception, 94(4):pp.328–339.

¹⁹ Reed, SK., DiBello, J., et al., (2021), 'Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17b-oestradiol (1.5mg) (PRO-E2 study): risk of venous and arterial thromboembolism', Eur J Contracept Reprod Health Care, 26(6):pp.439–446.

Table 6: Summary of estimated risk of VTE with COCs

COCs	Non-pregnant non-user	E4/DRSP	EE/DRSP	EE/LNG
Estimated risk of VTE per 10,000 women-years (trial or surveillance)	2	3.66 ^a	9-12 ^b	5-7 ^b
Odds ratio of VTE vs non-user (Overall estrogenicity)	Assumed 1	1.7 [#]	6.3 []	3.6 [*]
Relative risk of VTE vs non-user (based on nAPCsr)	Assumed 1	1.6	3.9 ^c	2.3

Source: Table 2.20, p70; and Table 2.22, p78, of the submission main body.

COC = combined oral contraceptive; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; EE/DRSP = ethinylestradiol 20 mcg/drospirenone 3 mg; EE/LNG = ethinylestradiol 30 mcg/levonorgestrel 150 mcg; nAPCsr = normalised activated protein C sensitivity ratio; VTE = venous thromboembolism.

^a Based on the overall estimated annual VTE incidence rate across the full E4/DRSP clinical program (pooled phase 2 and 3 trials).

^b Based on EMA/607314/2013

^c Based on the Cochrane review by de Bastos et al., 2014, assuming that EE/DRSP was equivalent to EE with cyproterone acetate

* Corrected during evaluation based on Section 2.7.1, p74 and Figure 2.7, p72 of the submission main body.

[#]Corrected from PSCR (p3)

6.45 During the July 2024 consideration of EE/DRSP (Yaz and Yasmin), the PBAC considered that the use of COCs is associated with an increased risk of VTE, and the risk has been shown to be slightly higher with COCs containing the progestogen drospirenone compared to those with levonorgestrel. However, the absolute risk of VTE in patients who use COCs is small (paragraph 7.7, drospirenone with ethinylestradiol, Public Summary Document (PSD), July 2024 PBAC Meeting). The PBAC noted evidence presented on VTE risk with the use of drospirenone, including information provided by the TGA²⁰ and Therapeutic Guidelines on oral contraceptives containing drospirenone, and systematic reviews by Bateson et al (2016)²¹ and Dragoman et al (2018)²² (paragraphs 6.30, 6.32, 6.33, 7.7, drospirenone with ethinylestradiol, PSD, July 2024 PBAC Meeting).

6.46 Douxfils et al. (2024)²³ suggested that VTE risk was reduced with natural oestrogen-based COCs, compared to synthetic oestrogen-based COCs which contained EE. However, this meta-analysis assessed the natural oestrogen estradiol, and none of the studies included E4.

²⁰ Therapeutic Goods Administration, (2011), 'Oral contraceptives containing drospirenone (Yaz and Yasmin)', accessed 14 January 2025. Available at www.tga.gov.au/news/safety-alerts/oral-contraceptives-containing-drospirenone-yaz-and-yasmin

²¹ Bateson, D., Butcher, B.E., et al., (2016), 'Risk of venous thromboembolism in women taking the combined oral contraceptive: A systematic review and meta-analysis', *Aust Fam Physician*, 45(1):pp.59-64.

²² Dragoman, M.V., Tepper, N.K., et al., (2018), 'A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception', *Int J Gynecol Obstet*, 141:pp.287-294.

²³ Douxfils J., Raskin L., Didembourg M., et al., (2024), 'Are natural estrogens used in contraception at lower risk of venous thromboembolism than synthetic ones? A systematic literature review and meta-analysis', *Front Endocrinol (Lausanne)*, 15:1428597.

Benefits/harms

6.47 The evidence presented in the submission did not allow for a quantitative comparison of the benefits and harms of E4/DRSP and other COCs listed on the PBS. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.48 The submission described E4/DRSP as superior in terms of specific longer-term safety such as the risk of VTE and the risk of MI and stroke compared to EE/LNG and EE/DRSP. This claim was uncertain due to the following reasons:

- There were no head-to-head studies directly comparing the risk of VTE, MI and stroke with E4/DRSP compared to EE/LNG and EE/DRSP.
- Instead, the submission relied on surrogate biomarkers examined in the MIT-Es0001-C201 study, which were mapped to the clinical outcomes reported in other studies which did not include E4/DRSP (Roach et al., 2015, de Bastos et al., 2014, Lidegaard et al., 2012 and Morimont et al., 2021).
- MIT-Es0001-C201, a phase II, open-label, single-centre study demonstrated a high risk of bias, and partially complied with the EMA ‘Guideline on clinical investigations of steroid contraceptives in women’ for the development of hormonal contraceptives to address safety concerns and rare risks (e.g., cardiovascular events and VTE).
- The published studies did not provide any evidence of the risk of VTE, or MI and stroke, with E4/DRSP.
- The approach of mapping to estimate the risk of VTE or MI and stroke was uncertain, and the magnitude of risk reduction from changes in surrogate biomarkers is unclear.
- Based on the Australian Public Assessment Report for E4/DRSP, the TGA considered the association between laboratory results (surrogate biomarkers) from the E4/DRSP trial and VTE risk to be weak, and concluded that no claims regarding the relative VTE risk of E4/DRSP compared to other COCs could be made based on the available data.

6.49 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.50 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

Economic analysis

6.51 The submission presented a cost-consequence analysis. The PBAC Guidelines (Version 5.0) state that cost-effectiveness should be estimated using a cost-effectiveness and/or a cost-utility analysis, and other economic evaluations such as a cost-

consequence analysis should not be presented as base-case analyses. However, it may be useful as a supplementary or preliminary analysis to a cost-effectiveness or cost-utility analysis. The submission justified that a cost-effectiveness analysis based on the cardiovascular benefits with E4/DRSP would be inappropriate given that the main purpose of E4/DRSP is for contraception. However, the cost-effectiveness of E4/DRSP can be estimated by translating the reduction in incidence of VTE into cost savings, and comparing these cost savings to the incremental cost of treatment with E4/DRSP (for further details, see paragraph 6.60).

6.52 In the absence of trial based comparative data, the submission presented long-term safety benefits of E4/DRSP against other COCs, using surrogate biomarkers from the MIT-Es0001-C201 study and published literature, to support the proposed price premium for E4/DRSP. The MIT-Es0001-C201 was a 6-cycle study, and such study duration was insufficient to support a long-term safety claim. The long-term safety benefits of E4/DRSP in the economic analysis focused on risk reduction in the incidence of MI and stroke and VTE compared to other COCs, and was similar to those presented above in the comparative harms section.

6.53 The incremental cost per year of E4/DRSP compared to the COCs PBS-listed at the time of the submission are summarised in Table 7.

Table 7: Incremental cost of E4/DRSP compared to other PBS-listed COCs

PBS item code	Combined oral contraceptive	Prescriptions required per year*	Percentage use ^a	DPMQ (\$)	Annual cost (\$)*
NA	E4 15 mg/DRSP 3 mg	4.35	100%		
1392G	EE 30 mcg/LNG 50 mcg & EE 40 mcg/LNG 75 mcg & EE 30 mcg/LNG 125 mcg	3.26	4.20%	21.18	69.05
1394J	EE 30 mcg/LNG 150 mcg	3.26	78.75%	17.87	58.26
1456P	EE 50 mcg/LNG 125 mcg	3.26	3.83%	23.33	76.06
2416E	EE 20 mcg/LNG 100 mcg	3.26	8.76%	19.57	63.80
2774B	EE 35 mcg/NETA 500 mcg	3.26	1.87%	24.81	80.88
2775C	EE 35 mcg/NETA 1 mg	3.26	2.59%	24.81	80.88
NA	Mestranol 50 mcg/ NETA 1 mg ^b	3.26	0.12%	24.81	80.88
Weighted average annual cost of comparator**					60.98
Incremental cost of E4/DRSP*					

Source: Table 4.2, p89; and Table 3.2, p83 of the submission main body.

COC = combined oral contraceptive; DPMQ = dispensed price for maximum quantity; DRSP = drospirenone; E4 = estetrol; EE = ethinylestradiol; LNG = levonorgestrel; mcg = micrograms; mg = milligrams; NA = not applicable; NETA = norethisterone; PBS = Pharmaceutical Benefits Scheme.

^a Based on PBS statistics for Year 2022 and 2023 provided in the Financial workbook to the submission.

^b No longer available on the PBS from 1 September 2023, and was discontinued from market since 30 April 2024.

*Number of prescriptions required per year was corrected from 4 to 4.35 and from 3 to 3.26 during the evaluation based on pack size and daily dosing.

**Corrected during evaluation to account for the updated DPMQ for PBS item 1392G.

6.54 The submission requested a Dispensed Price for Maximum Quantity (DPMQ) for E4/DRSP of \$. The requested DPMQ is higher than the DPMQ for other COCs currently

listed on the PBS and the private price available from an online pharmacy (\$82.99 for 3 packs).²⁴

- 6.55 Table 8 outlines the disaggregated cost and a range of outcomes presented by the submission to inform decision-making regarding the relative benefit of E4/DRSP compared to the PBS listed COCs.

Table 8: Disaggregated costs and benefit per patient for the cost-consequence analysis

COCs	E4/DRSP	EE/DRSP	EE/LNG
Odds ratio (risk of MI or stroke)	1.2	1.6	2.0 ^d /2.4 ^e
Impact on lipid profile	Same as baseline except a small increase in triglycerides	Increase in HDL and largest increase in triglycerides	Decrease in HDL and increase in triglycerides
Estimated risk of VTE per 10,000 women-years (trial or surveillance)	3.66 ^a	9-12 ^b	5-7 ^b
Odds ratio of VTE vs non-user (Overall estrogenicity)	1.4	6.3	3.6*
Relative risk of VTE vs non-user (based on nAPCs ^r)	1.6	3.9 ^c	2.3
Estimated costs	\$*	NA	\$58.26*

Source: Table 3.3, p84 of the submission main body.

COC = combined oral contraceptive; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; EE/DRSP = ethinylestradiol 20 mcg/drospirenone 3 mg; EE/LNG = ethinylestradiol 30 mcg/levonorgestrel 150 mcg; HDL = high density lipoprotein; MI = myocardial infarction; nAPCs^r = normalised activated protein C sensitivity ratio; NA = not available (at the time of submission); VTE = venous thromboembolism.

^a Based on the overall estimated annual VTE incidence rate across the full E4/DRSP clinical program (pooled phase 2 and 3 trials).

^b Based on EMA/607314/2013

^c Based on the Cochrane review by de Bastos et al., 2014, which found that EE/DRSP had the same risk as EE with cyproterone acetate – the value for EE with cyproterone acetate has therefore been used

^d Risk of MI/stroke was 2.0 for COC with 20 mcg of estrogen (Roach et al., 2015).

^e Risk of MI/stroke was 2.4 for COC with 30-49 mcg of estrogen (Roach et al., 2015).

*Corrected based on 4.35 prescriptions required per year for E4/DRSP (i.e. \$*4.35), and 3.26 prescriptions required annually for EE/LNG (i.e. \$17.87*3.26).

- 6.56 Figures in Table 8 were corrected during evaluation based on Section 2.7.1 and Figure 2.7 of the submission main body. To interpret the cost-consequence analysis from a cost-utility perspective, the submission presented the quality-adjusted life years (QALYs) gains required for E4/DRSP to be considered cost-effective. However, the submission left the judgement on whether the potential reductions in MI, stroke and VTE would translate to such QALY gains to the PBAC for its consideration.

- 6.57 Table 9 and Figure 4 present various ICER thresholds along with the QALY gains required for the incremental benefits of E4/DRSP to be cost-effective at the proposed price.

²⁴Chemist Warehouse, (2024), 'Nextstellis Tablets 84 (3 x 28) - Estetrol + Drospirenone', accessed 12 December 2024. Available at [www.chemistwarehouse.com.au/buy/118874/nextstellis-tablets-84-\(3-x-28\)---estetrol-drospirenone](http://www.chemistwarehouse.com.au/buy/118874/nextstellis-tablets-84-(3-x-28)---estetrol-drospirenone)

Table 9: QALY gains per year required for E4/DRSP to be cost-effective at the proposed price

ICER threshold (\$)	QALY gains per year required for E4/DRSP to be cost-effective at the proposed price
*1	0.0144
2	0.0115
2	0.0096
3	0.0082
3	0.0072
4	0.0064

Source: Table 3.4, p85 of the submission main body.

E4/DRSP = estetrol 15 mg/ drospirenone 3 mg; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

*Corrected during evaluation.

The redacted values correspond to the following ranges:

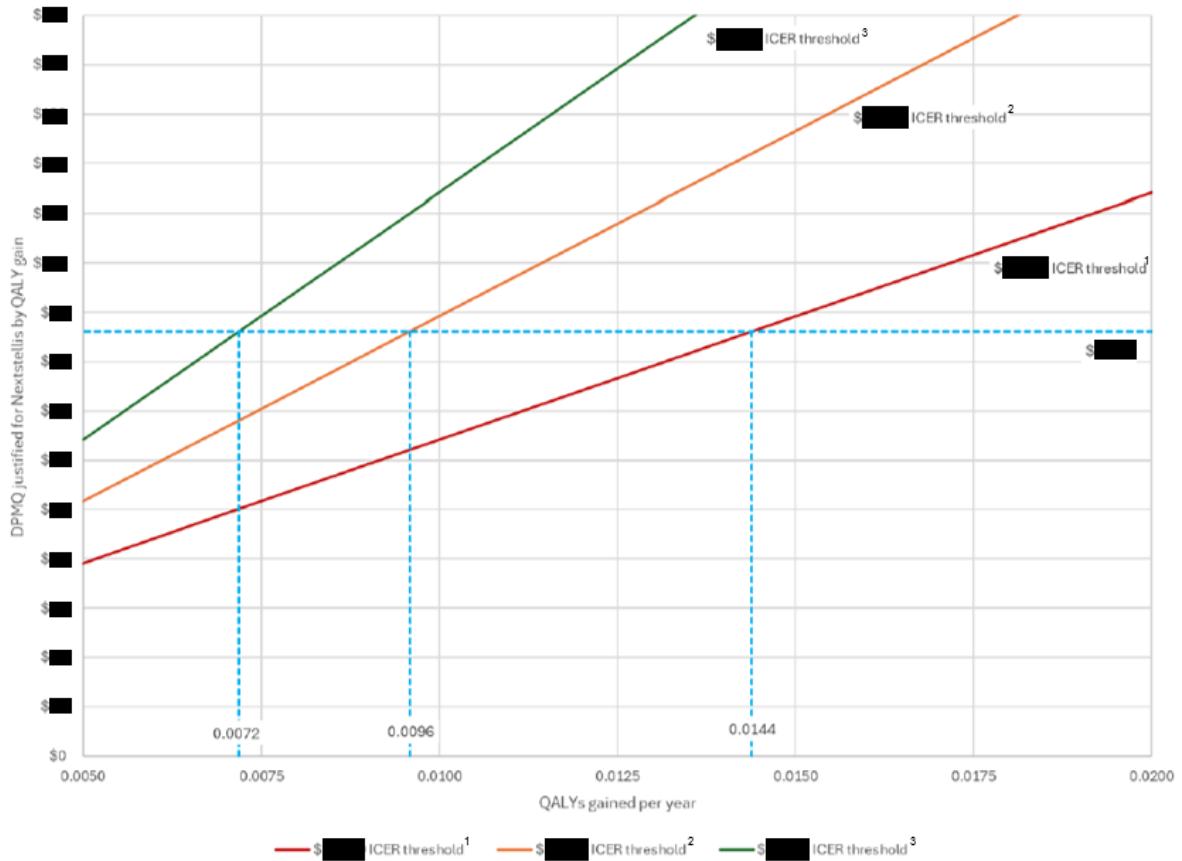
¹ \$15,000 to < \$25,000

² \$25,000 to < \$35,000

³ \$35,000 to < \$45,000

⁴ \$45,000 to < \$55,000

Figure 4: DPMQ justified for E4/DRSP at varying levels of QALY gain and ICER threshold



Source: Figure 3.1, p86 of the submission main body.

DPMQ = Dispensed Price for Maximum Quantity; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life years.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$25,000 to < \$35,000

³ \$35,000 to < \$45,000

- 6.58 The submission suggested that the proposed DPMQ for E4/DRSP at \$ [REDACTED] was justified when an ICER threshold of \$25,000 to < \$35,000/QALY was applied, where the gain of 0.0096 QALY/year was assumed to be realised with the use of E4/DRSP in terms of risk reduction in VTE and MI/stroke.
- 6.59 The approach used by the submission to justify the price premium of E4/DRSP over other COCs is oversimplified and lacks supporting evidence. The methodology of translating a cost-consequence analysis to a cost-utility framework is oversimplified, and it remains uncertain based on the presented approach how the reduction in the risk of MI and stroke and VTE with E4/DRSP would translate into QALY gains. Furthermore, as outlined in paragraph 6.47, the evidence presented for the claim of superior long-term safety in terms of the risk of MI, stroke and VTE was uncertain. In the absence of direct comparative evidence, the magnitude of this reduction was also uncertain, as the submission used surrogate biomarkers combined with existing risk estimates to examine the long-term cardiovascular safety of E4/DRSP compared to other COCs.
- 6.60 A scenario analysis was conducted during the evaluation to estimate the cost-effectiveness of E4/DRSP based on the claim of superior safety in reducing the risk of VTE. The approach used during evaluation translates the reduction in the incidence of VTE into cost savings, and compared these cost savings to the incremental cost of treatment with E4/DRSP.
- 6.61 Based on the estimated risk of VTE per 10,000 WY, presented in Table 10, E4/DRSP resulted in 1.34 less VTE events per 10,000 WY compared to EE/LNG. The number needed to treat (NNT) to avoid one case of VTE was estimated as 7,463 WY. The estimated cost of one year of treatment with E4/DRSP is \$ [REDACTED] and EE/LNG is \$58.26, resulting in an incremental cost of \$ [REDACTED]. Based on NNT, the incremental cost to avoid one case of VTE is > \$1,055,000 (7,463 WY x \$ [REDACTED]). According to the Access Economics report (2008)²⁵, the health expenditure per case of VTE in females aged 25–34 was estimated to be \$6,854 in Australia. Adjusted for inflation, this corresponded to \$9,882 in 2024 Australian dollars. A similar analysis was also performed using the upper bound of 7 VTE events per 10,000 WY with EE/LNG. The result of the scenario analysis is presented in Table 10.

²⁵ Access Economics, (2008), 'The burden of venous thromboembolism in Australia', accessed on 20 Nov 2024. Available at www.safetyandquality.gov.au/sites/default/files/migrated/Access-Economics_The-burden-of-VTE-in-Australia_2008.pdf

Table 10: Results of scenario analyses

Analyses	E4/DRSP	EE/LNG	Increment
Scenario 1 with an estimated 5 VTE cases per 10,000 WY in EE/LNG users			
Estimated VTE cases per 10,000 WY	3.66 ^a	5 ^b	-1.34
NNT with E4/DRSP to avoid one case of VTE			7,463 ^c
Annual cost of COC per woman	\$	\$58.26 ^d	\$
Incremental cost of E4/DRSP to avoid one case of VTE			\$ ^{e1}
Cost offset due to avoiding health expenditure of one VTE case			\$9,882 ^f
Net cost of one VTE case avoided due to use of E4/DRSP			\$ ¹
Scenario 2 with an estimated 7 VTE cases per 10,000 WY in EE/LNG users			
Estimated VTE cases per 10,000 WY	3.66 ^a	7 ^b	-3.34
NNT with E4/DRSP to avoid one case of VTE			2,994 ^g
Annual treatment cost per woman	\$	\$58.26 ^d	\$
Incremental cost of E4/DRSP to avoid one case of VTE			\$ ^{e2}
Cost offset due to avoiding health expenditure of one VTE case			\$9,882 ^f
Net cost of one VTE case avoided due to use of E4/DRSP			\$ ²

Source: Conducted during evaluation and adapted from Table 3.3, p84 of the submission main body.

ARR = absolute risk reduction; COC = combined oral contraceptive; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; EE/LNG = ethinylestradiol 30 mcg/levonorgestrel 150mcg; PBS = Pharmaceutical Benefits Scheme; NNT = number needed to treat; VTE = venous thromboembolism; WY = women-years.

^a the estimated annual VTE incidence rate in E4/DRSP trial (pooled phase 2 and 3 trials)

^b based on EMA/607314/2013²⁶

^c NNT = 1 / ARR, where ARR = control event rate – experimental event rate i.e. NNT = 1 / (0.0005 – 0.000366)

^d lowest cost PBS-listed COC i.e. EE 30 mcg / LNG 150 mcg with a DPMQ of \$17.87 (as of January 2025) for 112 tablets

^e Incremental annual cost of COC per woman multiplied by NNT

^f figure was inflated to 2024 price (using a conversion rate of 1.447, as estimated from purchasing power parities for Gross Domestic Product), based on the health expenditure per VTE case for females aged 25-34 of \$6,854 in year 2008, as reported in “The burden of venous thromboembolism in Australia”²⁵

^g NNT = 1 / ARR, where ARR = control event rate – experimental event rate i.e. NNT = 1 / (0.0007 – 0.000366)

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$855,000 to < \$955,000

6.62 The net cost of one case of VTE avoided with E4/DRSP use ranged from \$855,000 to < \$955,000 to > \$1,055,000.

Drug cost/patient/year: \$

6.63 For E4/DRSP, the estimated drug cost/patient per year would be \$, based on a DPMQ of \$ and 4.35 prescriptions per year (one pack containing three blister strips of 28 tablets with three repeats).

6.64 The drug cost/patient per year for the lowest cost COC currently listed on the PBS, that is, levonorgestrel 150 micrograms and ethinylestradiol 30 micrograms, is \$58.26, based on DPMQ of \$17.87 and 3.26 prescriptions per year (one pack containing four blister strips of 28 tablets with two repeats).

²⁶ European Medicines Agency, (2013), ‘PRAC confirms that benefits of all combined hormonal contraceptives continue to outweigh risks’, accessed 22 November 2024. Available at www.ema.europa.eu/en/documents/referral/prac-confirms-benefits-all-combined-hormonal-contraceptives-chcs-continue-outweigh-risks_en.pdf

Estimated PBS usage & financial implications

6.65 This submission was not considered by DUSC. The submission used a market share approach to estimate the financial impact of listing E4/DRSP on the PBS.

6.66 The key inputs and sources of data used in the financial estimates are presented in Table 11.

Table 11: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prescription utilisation		
Total number of prescriptions for COCs	6,249,076 ^a prescriptions in Year 1 to 6 based on IMS data for the year 2023 for EE/LNG sequential (1392G), EE 30 mcg /LNG 150 mcg (1394J), EE 20 mcg/LNG 125 mcg (1456P), EE 20 mcg/LNG 100 mcg (2416E), EE 35 mcg/NETA 500 mcg (2774B), EE 35 mcg/NETA 1,000 mcg (2775C), and MES 50 mcg/NETA 1,000 mcg (3179H)	The current market includes medicines below the general co-payment and would not be captured in the PBS/RPBS data, so the submission utilised the IQVIA/IMS dataset to calculate the script utilisation. However, the number of prescriptions proposed using the IMS dataset was significantly higher than those reported in the publicly available under-co-payment report (available from www.pbs.gov.au/info/statistics/under-co-payment/ucp-data-report). Consequently, this was likely overestimated. Additionally, the fixed-dose combination of NETA 1,000 mcg and MES 50 mcg is no longer listed on the PBS (removed 1 September 2023). The IMS dataset details were not adequately described in the submission. Additionally, the submission did not consider patients currently using Nextstellis privately.
Market growth rate	0%; based on Sponsor's assumption	This was uncertain; The IMS database included with the submission indicated a 10% decline in total number of units of COC from 2022 to 2023. If patients currently using privately listed COCs, including patients currently on private scripts for Nextstellis, were to substitute for E4/DRSP, the market growth rate may be larger than the sponsor assumed.
Market share	Increasing from █████% in Year 1 to █████% in Year 2 and Year 3, and further to █████% from Year 4 onwards; based on Sponsor's assumption	This was uncertain. Yaz and Yasmin were recommended by the PBAC at its July 2024 Meeting, and listed on the PBS in March 2025. Given the similar progestogen component (drospirenone), patients from the private market of Yaz and Yasmin may switch to E4/DRSP if it is listed on PBS. It is also possible that patients using other contraceptives privately may switch to Nextstellis if listed on the PBS.
Script equivalence	1.33 prescriptions; pack size of E4/DRSP provides three months of treatment compared to four months of treatment with other PBS-listed COCs	Due to the difference in pack size, there will be more frequent dispensing, along with associated dispensing fees, and a higher number of patient co-payments, compared to other PBS-listed COCs.
Costs		
Cost of comparators	LNG/EE (sequential preparation): \$24.81 LNG 150 mcg/EE 30 mcg: \$17.87	The submission used an incorrect DPMQ of \$24.81 instead of \$21.18 for LNG/EE (sequential

Public Summary Document – March 2025 PBAC Meeting

Parameter	Value applied and source	Comment
Prescription utilisation		
(Published DPMQ; 112-day supply)	LNG 125 mcg/EE 50 mcg: \$23.33	preparation), which was corrected during the evaluation. During the evaluation it was noted that there was a brand price premium, and a higher DPMQ, for some PBS-listed COCs such as the brand Triquilar ED. As this cost is borne by the consumer, this may affect the patient co-payment but not the cost to the PBS/RPBS. The fixed dose combination of NETA 1,000 mcg and MES 50 mcg is no longer listed on the PBS as of 1/09/2023. Some of these patients may have changed to an alternative PBS listed COC.
	LNG 100 mcg/EE 20 mcg: \$19.57	
	NETA 500 mcg/EE 35 mcg: \$24.81	
	NETA 1,000 mcg/EE 35 mcg: \$24.81	
	NETA 1,000 mcg/MES 50 mcg: \$24.81	
E4/DRSP	Requested DPMQ: \$ [REDACTED] for 84-day supply	The requested DPMQ for E4/DRSP was higher than the DPMQ for COCs currently listed on the PBS and the private price for E4/DRSP available from an online pharmacy (\$82.99 for 3 blister strips with 28 tablets each). ²⁴
Co-payment for comparators	PBS = \$18.30 and RPBS = \$7.18; based on the weighted average of the co-payment for all the comparators. If the co-payment amount exceeded the DPMQ, it was assumed to be equivalent to the DPMQ value.	The DPMQ for all other COCs listed on the PBS as of January 2025 are below the general co-payment.
Co-payment for E4/DRSP	PBS = \$31.60 and RPBS = \$7.70; based on PBS published co-payment values.	This was reasonable.

Source: Table 4.3, p90 and Table 4.5 p91 of the submission main body and Attachment 11 'Nextstellis_contraception_of utilisation financial implications_Mar2025_Mayne' to the submission.

COC = combined oral contraceptive; DPMQ = dispensed price for maximum quantity; DRSP = drospirenone; E4 = estetrol; EE = ethinylestradiol; LNG = levonorgestrel; mcg = micrograms; MES = mestranol; mg = milligrams; NETA = norethisterone; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^aCorrected during evaluation – incorrect utilisation for norethisterone and mestranol in cells I56:N56 of '2e. Scripts – market' worksheet as well as cell Y7 of the 'IMS data' worksheet of Attachment 11 'Nextstellis_contraception_Estimates of utilisation financial implications_Mar2025_Mayne' workbook.

6.67 Table 12 presents the estimated financial implications of listing E4/DRSP.

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 scripts dispensed*	1	1	1	2	2	2
Estimated financial implications of E4/DRSP						
Cost to PBS/RPBS less copayments*	\$3	\$4	\$4	\$5	\$5	\$5
Estimated financial implications for other PBS-listed COCs						
Cost to PBS/RPBS less copayments*	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Net financial implications						
Net cost to PBS/RPBS*	\$3	\$7	\$7	\$5	\$5	\$5

Source: Table 4.5, p91; Table 4.7, p92; Table 4.9, p94; Table 4.10, p95; Table 4.11, p96 of the submission main body and Attachment 11 'Nextstellis_contraception_Estimates of utilisation financial implications_Mar2025_Mayne' to the submission.

COC = combined oral contraceptive; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

*a Back calculated assuming 4.35 prescriptions per year.

*Corrected during evaluation for incorrect market share used in cells F167, F179 and incorrect utilisation for norethisterone and mestranol in cells I56:N56 of '2e. Scripts – market' worksheet as well as incorrect DPMQ for PBS Item code 1392G in cell Y7 of the 'IMS data' worksheet of Attachment 11 'Nextstellis_contraception_Estimates of utilisation financial implications_Mar2025_Mayne' workbook.

The redacted values correspond to the following ranges:

¹ 1,000,000 to < 2,000,000

² 2,000,000 to < 3,000,000

³ \$60 million to < \$70 million

⁴ \$90 million to < \$100 million

⁵ \$100 million to < \$200 million

⁶ net cost saving

⁷ \$80 million to < \$90 million

6.68 The net cost to the PBS/RPBS of listing E4/DRSP was estimated to be \$100 million to < \$200 million in Year 6, and a net cost of \$500 million to < \$600 million in the first 6 years of listing .

6.69 The utilisation/financial estimates for E4/DRSP were considered uncertain due to the following issues:

- The submission relied on the IQVIA/IMS database to estimate the utilisation of the COCs listed on the PBS. There were differences in the utilisation estimates derived from the IMS database and the PBS/RPBS services data given that the current market includes COCs below the general co-payment and would not be captured in the PBS/RPBS data. The estimates from the IMS data were significantly higher than the under-co-payment data report for the COCs listed on the PBS. Consequently, the market size, and therefore the financial implications of listing E4/DRSP, were likely overestimated.
- The submission assumed the market for COCs would remain stable, with a similar distribution of patients across the products over the next six years.
- This assumption was uncertain for a number of reasons that may increase or decrease the market size of PBS-listed COCs:
 - The most recent source of COC choices, Skiba et al. (2019), used data collected from 2016 to 2017. The IMS data provided in the submission showed a 10.3%

decline in total number of units of COC supplied from 2022 to 2023, indicating the submission overestimated the market growth.

- The utilisation of COCs on the PBS may increase should listing of additional COCs occur, increasing the affordability for patients. Most recently, Yaz and Yasmin were listed on the PBS in March 2025. Should more COCs be listed on the PBS the market size of PBS-listed COCs may grow at the expense of the private script market.
 - Assuming a 5% decline in usage led to a 17% reduction in net cost to the PBS/RPBS, while a 5% increase in usage resulted in a 21% increase in net cost to the PBS/RPBS (for further details, refer Table 13).
 - The submission did not provide any evidence to support the assumption of a $\frac{1}{2}$ % share of the COC market for E4/DRSP in Year 1, gradually increasing to $\frac{1}{2}$ % from Years 4-6. The PSCR estimated that, if Yaz and Yasmin were PBS-listed, the uptake rates for E4/DRSP could be $\frac{1}{2}$ % across 5 years of listing, however this was uncertain.
 - The submission did not account for the private market of E4/DRSP, which would transition to accessing E4/DRSP on the PBS if listed. According to the IMS data report, there were 20,000 to < 30,000 units sold in 2023, with an increase to 20,000 to < 30,000 by June 2024 for E4/DRSP.
 - Additionally, the submission did not account for the private market of other COCs. Based on the IMS data report, approximately 25% of the total units supplied were for COCs not listed on the PBS. This may underestimate the financial impact, particularly if patients on other private COCs switch to E4/DRSP if it is listed. Furthermore, given the same progestogen component (drospirenone), patients using Yaz and Yasmin on the private market may switch to E4/DRSP if it is listed. However, the proportion of such patients remains uncertain, as no comparative evidence is currently available.
 - The cost-offset associated with the listing of E4/DRSP may be overestimated, as the submission used the weighted average co-payment for all comparators. Given that the DPMQ for all other COCs currently PBS-listed is below the general co-payment, the actual cost-offset is likely to be smaller and primarily attributed to patients who reach the PBS safety net and concession patients.
- 6.70 Sensitivity analyses of the financial estimates were conducted during the evaluation, as summarised in Table 13.

Table 13: Sensitivity analysis of the Utilisation and Cost Model – Net cost to PBS/RPBS*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Percentage change from base case (%)
Base case	\$ ¹	\$ ²	\$ ²	\$ ³	\$ ³	\$ ³	-
Sensitivity analysis 1 – Inclusion of private script market							
Substitution of 100% of E4/DRSP private scripts	\$ ¹	\$ ⁴	\$ ⁴	\$ ³	\$ ³	\$ ³	+1%
Substitution of all private scripts at PBS market rates	\$ ²	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	+19%
Sensitivity analysis 2 – Alternative co-payment calculation							
	\$ ¹	\$ ²	\$ ²	\$ ³	\$ ³	\$ ³	+0.3%
Sensitivity analysis 3 – Market growth rate							
-10%	\$ ¹	\$ ⁵	\$ ¹	\$ ⁵	\$ ¹	\$ ⁶	-32%
- 5%	\$ ¹	\$ ²	\$ ⁵	\$ ⁴	\$ ²	\$ ²	-17%
+5%	\$ ⁵	\$ ⁴	\$ ³	\$ ³	\$ ³	\$ ³	+21%
+10%	\$ ⁵	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	+45%
Sensitivity analysis 4 – Change in market substitution rate							
-20%	\$ ⁶	\$ ⁵	\$ ⁵	\$ ²	\$ ²	\$ ²	-17%
+20%	\$ ²	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	+20%

Source: 'Nextstellis_contraception_Estimates of utilisation financial implications_Mar2025_Mayne' workbook

E4/DRSP = estetrol 15 mg/drospirenone 3 mg; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

*Calculated during the evaluation.

The redacted values correspond to the following ranges:

¹ \$60 million to < \$70 million

² \$80 million to < \$90 million

³ \$100 million to < \$200 million

⁴ \$90 million to < \$100 million

⁵ \$70 million to < \$80 million

⁶ \$50 million to < \$60 million

- 6.71 The financial estimates were highly sensitive to the rate of market growth, market substitution rate and substitution of private prescriptions. The results were largely unaffected when considering an alternative co-payment calculation method and complete substitution of current private E4/DRSP scripts.
- 6.72 The PSCR acknowledged there were uncertainties in the financial estimates provided, and stated this was due to a number of reasons, including different pack sizes between PBS-listed and private oral contraceptives, the General price for PBS-listed oral contraceptives being below the patient co-payment meaning PBS data reporting was incomplete, and data of contraceptive choices of Australian women derived from older surveys. The PSCR claimed the data presented in the submission could be a reasonable estimate of the market, but acknowledged the market uptake rates for E4/DRSP may be reduced if other oral contraceptives are listed on the PBS.
- 6.73 The PBAC noted the estimated use and financial implications were high, and higher than the estimated financial implications for other newer oral contraceptive pills that had been recommended for PBS-listing. Due to the discrepancy in the estimates between this submission and those for other newer oral contraceptive pills considered

by the PBAC, and to address some of the uncertainties in paragraph 6.68, revised financial estimates were done to provide a consistent approach to estimates for other similar submissions (Table 14). The revised estimates used the submission’s requested DPMQ of \$.

Table 14: Revised estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	1	2	2	2	2	2
Estimated financial implications of E4/DRSP						
Cost to PBS/RPBS less copayments*	\$3	\$3	\$3	\$3	\$3	\$3
Estimated financial implications for other PBS-listed COCs						
Cost to PBS/RPBS less copayments	-\$4	-\$4	-\$4	-\$4	-\$4	-\$4
Net financial implications						
Net cost to PBS/RPBS*	\$3	\$3	\$3	\$3	\$3	\$3

COC = combined oral contraceptive; E4/DRSP = estetrol 15 mg/drospirenone 3 mg; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ 90,000 to < 100,000

² 100,000 to < 200,000

³ \$0 to < \$10 million

⁴ net cost saving

6.74 The revised estimated use and financial implications in Table 14 adopt a similar approach to that taken for estimated use and financial implications for other newer oral contraceptive pills considered by the PBAC:

- The utilisation estimates from the IMS database, provided in the submission, for the PBS-listed pharmaceutical items was removed.
- Private scripts for E4/DRSP were included in the estimates, with 100% uptake rate applied to this private market. The private market was extrapolated into 12 months service volume based on the January – June 2024 IMS data for Nextstellis provided in the submission and multiplied by 2.

6.75 Based on the revised financial estimates, the net cost to the PBS/RPBS of listing E4/DRSP was estimated to be \$0 to < \$10 million in Year 6, and a net cost of \$30 million to < \$40 million in 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 estetrol with drospirenone (E4/DRSP) as an Unrestricted Benefit. The PBAC’s recommendation for listing was based on its assessment that the cost-effectiveness of E4/DRSP would be acceptable if it were cost-minimised against newer combined oral contraceptives (COCs) such as ethinylestradiol with drospirenone (EE/DRSP)(Yaz and Yasmin).

7.2 The PBAC considered COCs listed on the PBS, including ethinylestradiol/drospirenone,

to be appropriate comparators.

- 7.3 The PBAC noted the submission and sponsor hearing claimed that E4/DRSP is superior to PBS-listed and near market COCs, in terms of longer-term safety risks such as VTE and the risk of MI and stroke. The PBAC noted the evidence provided to support the claim of superior safety relied on surrogate biomarkers, and no head-to-head studies were provided that directly compared the risk of VTE, MI and stroke with E4/DRSP compared to other COCs. The PBAC noted that the EMA 'Guideline on clinical investigation of steroid contraceptives in women' advises that there are no generally accepted surrogate endpoints for the risk of cardiovascular events or VTE, and that the TGA considered the association between laboratory results from the E4/DRSP trial and VTE risk to be weak and that no claims regarding the relative VTE risk of E4/DRSP compared to other COCs could be made on the data available. The PBAC considered that the evidence provided did not support that E4/DRSP offered superior safety compared to COCs currently listed on the PBS.
- 7.4 The PBAC noted consumer comments highlighting equity and access issues, and that it is important that there are more affordable contraceptive options available to women. The PBAC also noted consumer comments received that stated that E4/DRSP offers a range of benefits to patients, including effective contraception and menstrual management, and a more tolerable safety profile compared to older oral contraceptive pills.
- 7.5 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.
- 7.6 The PBAC noted information provided in the sponsor hearing that in trials E4/DRSP had a slightly higher Pearl Index in women with a BMI of 30-35 kg/m² compared to women with a lower BMI, demonstrating a small reduction in efficacy. However, the PBAC was satisfied that the Pearl Index seen in women with the higher BMI still showed acceptable contraceptive efficacy and therefore provided effective contraception in this patient group.
- 7.7 The PBAC considered that E4/DRSP provides an additional COC option for individuals, and has non-inferior contraceptive efficacy compared to other COCs PBS-listed. The PBAC therefore recommended listing E4/DRSP on a cost-minimisation basis to other newer oral contraceptive pills. The PBAC advised the equi-effective doses are 28-day cycle of E4/DRSP \equiv 28-day cycle of EE 20 microgram/DRSP 3 mg / 28-day cycle of EE 30 microgram/DRSP 3 mg.
- 7.8 The PBAC advised that E4/DRSP is suitable for prescribing by nurse practitioners and endorsed midwives.
- 7.9 The PBAC noted the estimated use and financial implications of listing E4/DRSP on the PBS provided in the submission, and that there was an estimated net cost to the

PBS/RPBS of \$500 million to < \$600 million in the first 6 years of listing. The PBAC noted that this was higher than the estimated financial implications for other newer oral contraceptive pills that have been recommended for PBS-listing. The PBAC considered the estimated usage and financial estimates to be high.

- 7.10 The PBAC noted that for the financial estimates provided in the submission, the market share approach used to estimate the financial impact utilised IQVIA/IMS (private market) data to calculate the script utilisation, and included different brands of pharmaceutical items in the private market. This was a different approach than what was used to estimate utilisation and financial estimates for other newer oral contraceptive pills. The estimated number of scripts provided in the submission was higher than the estimated script numbers in other submissions for newer oral contraceptive pills.
- 7.11 The PBAC considered the revised financial estimates that removed utilisation estimates from the IMS database and included private scripts for E4/DRSP (Table 14), to be more reasonable estimates of the use of E4/DRSP. However, the PBAC advised that overall there were uncertainties in the uptake and use of newer oral contraceptive pills that are listed on the PBS, and therefore uncertainties in the financial implications of their listings. The PBAC advised that it will closely monitor the usage of newer oral contraceptive pills on the PBS and their financial impact. The PBAC reiterated 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, PSD, July 2024 PBAC Meeting with November 2024 Addendum).
- 7.12 The PBAC recommended that E4/DRSP should be treated as interchangeable on an individual patient basis with COCs containing EE/DRSP currently listed on the PBS.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because E4/DRSP 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.
- 7.14 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
ESTETROL + DROSPIRENONE					
estetrol 14.2 mg + drospirenone 3 mg tablet [24] (& inert substance tablet [4], 3 x 28	NEW	1	3	3	Nextstellis
Restriction Summary / Treatment of Concept:					
	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 welcomes the decision of the PBAC and looks forward to providing ESTETROL + DROSPIRENONE (Nextstellis®) on the PBS.