

5.09 ESTRADIOL

Transdermal gel (pump pack) 750 microgram (as hemihydrate) per 1.25 g dose, 64 doses, Estrogel[®]

5.18 PROGESTERONE

Capsule 100 mg, Prometrium[®]

5.10 ESTRADIOL AND PROGESTERONE

Pack containing transdermal gel (pump pack) estradiol 750 micrograms (as hemihydrate) per 1.25 g dose, 64 doses and 30 capsules progesterone 100 mg (micronised) Estrogel[®] Pro

Besins Healthcare Australia Pty Ltd

1 Purpose of submission

- 1.1 The Category 2 submissions requested General Schedule unrestricted benefit listings for estradiol transdermal gel (pump pack) 750 micrograms (as hemihydrate) per 1.25 gram dose (hereinafter referred to as Estrogel[®]), progesterone capsule 100 mg (hereinafter referred to as MP), and the combination pack of estradiol transdermal gel (pump pack) with MP (hereinafter referred to as Estrogel Pro), and corresponding General Schedule restricted benefit listings for 60-day maximum dispensed quantities (MDQ).
- 1.2 Listing for Estrogel was requested on the basis of a cost-minimisation approach (CMA) versus estradiol gel sachets 1 mg/g (Sandrena[®]). Listing for MP was requested on the basis of a cost-effectiveness analysis (CEA) versus medroxyprogesterone acetate (MPA) 5 mg or 10 mg. Listing for Estrogel Pro was requested on the basis of a CMA versus individual components of the combination pack, i.e. Estrogel and MP.

Table 1: Key components of the clinical issue for EstroGel addressed by the submission

Component	Description
Population	Women with symptoms of estrogen deficiency seeking MHT.
Intervention	EstroGel, estradiol (as hemihydrate) 0.06% w/w gel. Each pump of EstroGel delivers 1.25 g of gel, which contains 0.75 mg of estradiol. Recommended daily dose is 2 pumps (2.5 g of gel; 1.5 mg estradiol) Dose range: 1-4 pumps of gel (1.25-5 g gel; 0.75-3.0 mg estradiol).
Comparator	Sandrena, estradiol 0.1% w/w gel Recommended daily dose is 1.0 mg estradiol per day Dose range: 0.5 mg – 1.5 mg estradiol.
Outcomes	Reduction in the frequency of moderate to severe hot flushes (primary efficacy outcome) Reduction in the frequency and severity of all hot flushes Tolerability and safety, including the incidence of estrogen-related AEs of breast pain, breast tenderness and breakthrough bleeding.
Clinical claim	For the treatment of troublesome menopausal vasomotor symptoms in women, EstroGel 2.5 g is similar at reducing the frequency of moderate to severe hot flushes, compared to Sandrena 1.0 g. For the treatment of troublesome menopausal vasomotor symptoms in women, EstroGel 1.25 g is similar at reducing the frequency of moderate to severe hot flushes, compared to Sandrena 0.5 g. EstroGel 2.5 g is as safe and well tolerated as Sandrena 1.0 g. EstroGel 1.25 g is as safe and well tolerated as Sandrena 0.5 g. In addition to the main clinical claim, EstroGel also has the following benefit, compared to Sandrena: <ul style="list-style-type: none"> • prevention of osteoporosis in postmenopausal women at high risk of future fractures.

Source: Table 1.2, pp23-24 of the submission main body.

AE = adverse event; MHT = menopause hormone therapy; w/w = weight concentration.

Note: unopposed estradiol is indicated for use in women who have had a hysterectomy. Women with an intact uterus should be given progestogens for at least 12 days a month.

Table 2: Key components of the clinical issue for MP addressed by the submission

Component	Description
Population	Women with an intact uterus receiving treatment with estrogen for the symptoms of menopause.
Intervention	MP 100 mg capsule. Recommended daily dose: 200 mg/day for 12 days in the last half of each therapeutic cycle, beginning on day 15 and ending on day 26 (cyclical); or 100 mg/day from day 1 to day 25 of each therapeutic cycle (continuous).
Comparator	MPA 5 or 10 mg tablet. Recommended daily dose: 10 mg/day to 20 mg/day for at least 10 days of each cycle (cyclical); or 5 mg per day for 28 days of each cycle (continuous).
Outcomes	Endometrial hyperplasia (primary efficacy outcome), menopausal symptoms Tolerability and safety, including breast cancer (primary safety outcome) and bleeding patterns.
Clinical claim	MP is similar to MPA at protecting against the development of estrogen-associated endometrial hyperplasia in menopausal women with an intact uterus receiving combination MHT. MP is similar to MPA in terms of preserving the effectiveness of estrogen at treating menopausal symptoms in menopausal women with an intact uterus receiving combination MHT. MP may be superior to MPA and norethisterone at reducing the risk of progestogen-associated breast cancer in menopausal women with an intact uterus receiving combination MHT. MP has similar safety to MPA in terms of the side effects of treating menopausal symptoms in menopausal women with an intact uterus receiving combination MHT.

Source: Table 1.2, pp23-24 of the submission main body.

AE = adverse event; MHT = menopause hormone therapy; MP = micronised progesterone; MPA = medroxyprogesterone acetate.

Table 3: Key components of the clinical issue for Estrogel Pro addressed by the submission

Component	Description
Population	Women with an intact uterus with symptoms of estrogen deficiency seeking MHT.
Intervention	Estrogel Pro, combination pack of Estrogel and MP.
Comparator	Estrogel and MP in combination, dispensed as individual components.
Outcomes	Estrogen-related outcomes: Reduction in the frequency of moderate to severe hot flushes (primary efficacy outcome), reduction in the frequency and severity of all hot flushes, tolerability and safety, including the incidence of estrogen-related AEs of breast pain, breast tenderness and breakthrough bleeding. Progestogen-related outcomes: Endometrial hyperplasia (primary efficacy outcome), menopausal symptoms, tolerability and safety, including breast cancer (primary safety outcome) and bleeding patterns.
Clinical claim	As a combination pack, the clinical claim relies on the evaluation of the individual components, Estrogel and Prometrium. As such, a separate clinical evaluation is not presented. The clinical claim is as follows: In women with an intact uterus with symptoms of estrogen deficiency seeking MHT, Estrogel Pro medicine pack is equivalent to the individual components of Estrogel and Prometrium administered in combination, in terms of efficacy and safety.

Source: Table 1.2, pp23-24 of the submission main body.

AE = adverse event; MP = micronised progesterone; MHT = menopause hormone therapy.

2 Background

Registration status

- 2.1 Estrogel was Therapeutic Goods Administration (TGA) registered on 8 May 2019 for the following indications:
- Hormone replacement therapy for estrogen deficiency symptoms in postmenopausal women.
 - Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.
- 2.2 MP was TGA registered on 20 June 2016 for the following indications:
- Treatment of menstrual irregularities in women with menstrual abnormalities or secondary amenorrhoea due to normogonadotrophic amenorrhoea.
 - Hormone replacement therapy – for adjunctive use with an estrogen in postmenopausal women with an intact uterus.
- 2.3 Estrogel Pro was TGA registered on 23 October 2019 as a ‘Medicine Kit’ consisting of two components, Estrogel and MP. It is indicated for hormone replacement therapy for estrogen deficiency symptoms in post-menopausal women (Estrogel component) and hormone replacement therapy – adjunctive use with estrogen in post-menopausal women with an intact uterus (Prometrium component).

Senate inquiry into the issues related to menopause and perimenopause

- 2.4 The submission claimed that listing Estrogel, Prometrium and Estrogel Pro on the PBS would address the terms of the Senate inquiry into the issues related to menopause

and perimenopause, specifically the reference term ‘the level of awareness amongst medical professionals and patients of the symptoms of menopause and perimenopause and the treatments, including the affordability and availability of treatments’.

2.5 The Pre-Sub-Committee Response (PSCR) noted the following recommendations from the inquiry report¹:

- Recommendation 16: The committee recommends that the Department of Health and Aged Care, including the Therapeutic Goods Administration, consider action to address the shortages of menopause hormonal therapy (MHT) in the Australian market and consider options to secure sufficient supply, including a review of the supply chains and pricing trends of MHT, with a view to enabling universal affordable access to treatment and care.
- Recommendation 18: The committee recommends that the Australian Government examine options to implement a means of ensuring that MHT items are affordable and accessible, including consideration of domestic manufacturing and alternate means of subsidising costs to the consumer. Such examination should include, but not be limited to, considering ways to encourage pharmaceutical sponsors to list a broader range of MHT items, such as body identical hormone therapy products, on the Pharmaceutical Benefits Scheme to ensure appropriate access and lowered costs for all women who need it.
- Recommendation 19: The committee recommends that the Pharmaceutical Benefits Advisory Committee (PBAC) reforms comparator selection during evaluation of new MHT items to include quality of life health impacts. The committee also recommends that the PBAC regards body identical hormone therapy products in a separate drug class to remove the lowest cost comparator to synthetic therapies.

The PSCR also referred to comments in the report from practitioners regarding the cost of MHT products being prohibitive and the better safety profile of MP. The PSCR claimed that listing these products on the PBS would address recommendations from the inquiry.

¹ Commonwealth of Australia, (2024), ‘The Senate Community Affairs Reference Committee: Issues related to menopause and perimenopause’, available at: www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Menopause/Report

National Women’s Health Strategy 2020-2030

2.6 The submission referred to the *National Women’s Health Strategy 2020-2030*², and stated that listing Estrogel, Prometrium and Estrogel Pro on the PBS would align with the following priority areas:

- Priority area 1 action ‘Remove barriers to support equitable access to timely, appropriate and affordable care for all women, including culturally and linguistically sensitive and safe care’.
- Priority area 2 action ‘Support women and their health care providers to manage the effects of menopause’.

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

3 Requested listing

3.1 The submissions requested the following new listings. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL					
Estradiol 0.06% (as hemihydrate) gel, 1 x 80 g estradiol 0.06% (750 microgram/actuation) gel, 64 actuations	\$	1	1	5	Estrogel
Restriction Summary: Unrestricted / Treatment of Concept: NEW					
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					
Administrative Advice: <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>					
Administrative Advice: Estradiol should be used in conjunction with an oral a progestogen in women with an intact uterus.					

² Department of Health, (2018), ‘National Women’s Health Strategy 2020-2030’, Department of Health, Canberra. Available at: www.health.gov.au/resources/publications/national-womens-health-strategy-2020-2030?language=en

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MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL					
Estradiol 0.06% (as hemihydrate) gel, 4x 80 g estradiol 0.06% (750 microgram/actuation) gel, 64 actuations	\$	2	2	5	Estrogel
Restriction Summary: 14238 / Treatment of Concept: 14238					
	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"/> Restricted benefit				
	Administrative Advice: <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>				
	Administrative Advice: Estradiol should be used in conjunction with an oral a progestogen in women with an intact uterus.				
	Indication: The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient.				

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PROGESTERONE					
Progesterone (micronised) 100 mg soft capsules, 30	\$	1	30	5	Prometrium 100
Restriction Summary: Unrestricted / Treatment of Concept: NEW					
	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				
	Administrative Advice: <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>				

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PROGESTERONE					
Progesterone (micronised) 100 mg soft capsules, 30	\$	2	60	5	Prometrium 100
Restriction Summary: 14238 / Treatment of Concept: 14238					
	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"/> Restricted benefit				
	Administrative Advice:				

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	For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
	Indication: The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL AND PROGESTERONE					
Estradiol 0.06% (as hemihydrate) gel [80 g] & progesterone (micronised) 100 mg soft capsules [30], 1 pack progesterone 100 mg capsule [30] (&) estradiol 0.06% (750 microgram/actuation) gel [65 actuations], 1 pack	\$	1	1	5	EstroGel Pro
Restriction Summary: Unrestricted / Treatment of Concept: NEW					
	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				
	Administrative Advice: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.				

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL AND PROGESTERONE					
Estradiol 0.06% (as hemihydrate) gel [80 g] & progesterone (micronised) 100 mg soft capsules [30], 1 pack progesterone 100 mg capsule [30] (&) estradiol 0.06% (750 microgram/actuation) gel [65 actuations], 1 pack	\$	2	2	5	EstroGel Pro
Restriction Summary: 14238 / Treatment of Concept: 14238					
	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"/> Restricted benefit				
	Administrative Advice: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.				
	Indication: The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient.				

- 3.2 The requested quantity of 1 x 80 g gel pack for Estrogel is sufficient to provide 32 days of treatment at the usual recommended starting dose (two pumps (2.5 g) daily). The Product Information (PI) states that while some patients will respond to 1.25 g daily, the most usual starting dose is 2.5 g daily which will be effective for the majority of women. However, if patients do not experience effective relief after 1 month of treatment, the dosage may be increased to a maximum of 5 g daily.
- 3.3 The recommended dose for Prometrium for MHT is 200 mg daily at bedtime for 12 days in the last half of each therapeutic cycle (from days 15 to 26 inclusive). An alternative dose is Prometrium 100 mg at bedtime for days 1-25 of each therapeutic cycle. The requested quantity for Prometrium is sufficient to provide treatment for one treatment cycle, with 5-6 capsules left over.
- 3.4 The requested quantity for Estrogel Pro aligns with the quantities requested for the individual components. It will therefore provide sufficient quantity for approximately 1 month of treatment, with some medicine left over.
- 3.5 The requested maximum repeats will provide sufficient coverage for 6 months of treatment for the Unrestricted benefit listings. The requested maximum quantities and repeats for the 60-day MDQ Restricted benefit listings will provide sufficient quantity and coverage for 12 months of treatment.
- 3.6 The requested maximum quantities and repeats are consistent with the current listings for estradiol gel (Sandrena), combination MHT products: oral tablet Femoston 2/10 (estradiol and dydrogesterone); and patches containing estradiol and norethisterone (Estalis Continuous 50/140, Estalis Continuous 50/250, Estalis Sequi 50/140 and Estalis Sequi 50/250), which provide sufficient quantity for approximately 1 month of treatment as unrestricted benefit listings, and have corresponding 60-day MDQ Restricted benefit listings. The current PBS listings for norethisterone 5 mg tablets and medroxyprogesterone 5 mg and 10 mg tablets that are not restricted by indication have 60-day MDQ Restricted benefit listings. The quantities for the Unrestricted benefit listings for these items will provide sufficient quantity for at least 4 weeks, however this will vary due to different dose ranges and dosage regimens used.
- 3.7 The submission requested medical practitioners and nurse practitioners be included as authorised prescribers for Estrogel, Prometrium and Estrogel Pro, and stated that this would support increased patient access to these medicines. The current PBS listings for estradiol gel (Sandrena), combination MHT products: oral tablet Femoston 2/10 (estradiol and dydrogesterone); and patches containing estradiol and norethisterone (Estalis Continuous 50/140, Estalis Continuous 50/250, Estalis Sequi 50/140 and Estalis Sequi 50/250); norethisterone 5 mg tablets and medroxyprogesterone 5 mg and 10 mg tablets include nurse practitioners as authorised prescribers for continuing therapy only.
- 3.8 The submission requested the following Administrative Advice be included in the Estrogel listing: Estradiol should be used in conjunction with an oral progestogen in

women with an intact uterus. This is consistent with the caution included in the current PBS listings for estradiol gel (Sandrena) and estradiol patches 25 mcg/24 hours, 37.5 mcg/24 hours, 50 mcg/24 hours, 75 mcg/24 hours and 100 mcg/24 hours.

- 3.9 At its July 2024 meeting, when recommending estradiol 500 mcg gel sachets for PBS listing, the PBAC recommended the following Administrative Advice and that it be flowed on to other estradiol gel and patch products to replace the current advice: Estradiol should be used in conjunction with progestogen in women with an intact uterus. The PBAC was asked to advise if this revised advice should also be included for Estrogel, if recommended for PBS listing.

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

4 Population and disease

- 4.1 Menopause is defined as the permanent cessation of ovarian function. The average age of natural menopause has been reported at 51 years, with a range between the ages of 45 and 55 years. Surgical menopause occurs as a result of bilateral oophorectomy (removal of both ovaries). About 5% of women can have an early menopause (below 45 years) and 1% of women can have premature ovarian insufficiency (below 40 years).
- 4.2 During menopause, the loss of ovarian follicles and cessation of follicular development and ovulation leads to the end of cyclical estrogen and progesterone production. This reduction in estrogen can result in a spectrum of symptoms, with only 20% of women reporting no symptoms. Approximately 75% of women experience symptoms during perimenopause and post-menopause, with 25% experiencing moderate to severe symptoms. The most common symptoms include vasomotor symptoms (such as hot flashes, night sweats), joint and muscle pain, mood changes, sleep disturbances, low libido, and genitourinary symptoms. Menopause is also associated with an increased risk of osteoporosis and cardiovascular disease. These symptoms are linked to a decline in both health-related and menopause-specific quality of life.
- 4.3 MHT encompasses both unopposed estrogen use for women who have undergone hysterectomy and combined estrogen-progesterone therapy for women with an intact uterus who require progesterone to prevent endometrial hyperplasia and reduce the risk of endometrial cancer. MHT is effective in alleviating vasomotor symptoms (VMS), genitourinary symptoms of menopause (GSM), preventing bone loss, managing premature hypoestrogenism, and treating moderate to severe vulvovaginal symptoms. There are multiple formulations, dosages, and delivery methods available for MHT, including tablets, patches, and gels. Since both the effectiveness and risk-benefit profiles vary by formulation and delivery route, therapy

should be individualised based on each patient’s characteristics and personal preferences.³

- 4.4 EstroGel contains the active ingredient estradiol (as hemihydrate) 0.06% w/w gel. Estradiol is identical to endogenous estradiol, a potent estrogenic hormone, produced by the ovaries. MP soft capsules contain 100 mg or 200 mg micronised progesterone (only the 100 mg capsules are being considered for PBS listing), which is structurally similar to natural progesterone. EstroGel Pro is a combination pack consisting of EstroGel and MP.
- 4.5 The submission positioned EstroGel as an alternative option for women in whom an estrogen transdermal gel is considered most clinically appropriate. MP was positioned as an alternative option for women in whom an oral progestogen tablet or capsule is considered most clinically appropriate (for use with a single component estrogen). Lastly, EstroGel Pro was positioned as an alternative to the single components EstroGel and MP. However, as outlined below in paragraph 5.2, other PBS-listed MHTs, particularly PBS-listed estradiol patches, could be replaced in clinical practice for various reasons, including ongoing supply shortages in Australia.⁴
- 4.6 The Economics Sub Committee (ESC) noted the requested population for MP (women with an intact uterus receiving treatment with estrogen for the symptoms of menopause) was inconsistent with the requested population for estradiol (women with symptoms of estrogen deficiency seeking MHT). The requested population for estradiol includes use in women in perimenopause and where the timing of menopause is unclear. Furthermore, the ESC considered the outcome of ‘menopausal symptoms’ for MP was less specific than the outcomes proposed for estradiol. The ESC noted that the proposed listings were unrestricted, and that patient access would therefore not be affected.

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

5 Comparator

EstroGel

- 5.1 The submission nominated Sandrena gel (estradiol 0.1% [1 mg/g] gel) as the main comparator. The main argument provided in support of this nomination was that Sandrena gel is the only estrogen transdermal gel listed on the PBS for MHT. Additionally, according to Therapeutic Relativity Sheets, Sandrena gel is considered equivalent to estradiol patches releasing 50 micrograms estradiol every 24 hours at

³ Madsen T., Sobel T., Negash S., et al., (2023), ‘A Review of Hormone and Non-Hormonal Therapy Options for the Treatment of Menopause’, *Int J Womens Health*, 15, pp.25-836, <https://doi.org/10.2147/IJWH.S379808>

⁴ Therapeutic Goods Administration (TGA), (2024), ‘About the shortage of transdermal HRT patches’. Available at: www.tga.gov.au/about-HRT-shortages

appropriate dosages. This was reasonable, assuming the target population is women in whom an estrogen transdermal gel is considered most clinically appropriate.

- 5.2 For the requested population i.e., women seeking MHT for estrogen deficiency, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: estradiol patches 25 microgram/24 hours, 37.5 microgram/24 hours, 50 microgram/24 hours, 75 microgram/24 hours, 100 microgram/24 hours. The ESC noted that oral forms of estrogen have a higher risk of venous thromboembolism (VTE) compared to transdermal estrogen, and that oral estrogen is contraindicated in patients with risk factors for VTE or cardiovascular disease, elevated triglycerides, liver disease or gallbladder disease. The ESC noted that transdermal estrogen is recommended in these situations. The ESC therefore considered estradiol patches to be appropriate alternative comparators, but not estradiol tablets.

Micronised Progesterone

- 5.3 The submission nominated MPA 5 mg or 10 mg tablets as the main comparator, with norethisterone 5 mg tablets (hereinafter referred to as norethisterone) as the secondary comparator. The main argument provided in support of this nomination was that, although MP may replace both MPA and norethisterone in practice, MPA had higher utilisation for MHT in 2024. Additionally, direct evidence is available comparing MP with MPA. This was reasonable, assuming the target population includes women in whom an oral progesterone tablet or capsule is considered most clinically appropriate (for use with a single component estrogen).

EstroGel Pro

- 5.4 The submission nominated the single component of EstroGel with single component MP administered concomitantly as the main comparator. The main argument for this nomination was that if listed on the PBS, EstroGel Pro will provide an alternative to single component EstroGel and MP, thereby further reducing the cost of MHT for both patients and Government.
- 5.5 The following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: combination MHT patches with estradiol and norethisterone (Estalis® Continuous 50/140, Estalis Continuous 50/250, Estalis Sequi 50/140, Estalis Sequi 50/250). Additionally, PBS-listed estrogen preparations in combination with a PBS-listed progesterone could be alternative comparators.
- 5.6 The ESC considered other forms of MHT would be more appropriate comparators (e.g. combination MHT patches) and highlighted that the individual components (i.e., EstroGel and Prometrium) are the same product, and therefore not true comparators.

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 noted patients will often need to try different MHT products before finding the product most suitable for them, and it was important to have a range of products available on the PBS. The clinician also noted there have been shortages of MHT products, and it was therefore important to have supply of MHT products that are locally produced.
- 6.2 The clinician stated there were a range of benefits of EstroGel and Prometrium compared to MHT products currently PBS-listed, and there was increasing evidence and expert opinion on the superior safety of MP compared to other progestogens, and transdermal estrogen compared to oral forms. The clinician noted these products are currently available on the private market however come with an increased cost to patients, and the cost limited women accessing these products. If these products were PBS-listed it would increase affordability for patients and address equity and access issues.
- 6.3 The clinician noted a transdermal estrogen gel product is available on the PBS, but stated this product has disadvantages, including needing to air dry before patients get dressed, it can feel sticky (even after drying), and can be unpleasant under clothing. The clinician stated EstroGel has a number of benefits, including being an alcohol-based product which dries quickly on the skin without leaving a sticky or unpleasant residue, and the pump pack allows for more flexible dosing when patients are titrating doses compared to the fixed dose sachets of the estradiol product currently PBS-listed. The clinician noted that EstroGel also has a TGA-registered indication for osteoporosis, however the estradiol gel product currently PBS-listed does not have this indication, and stated it was valuable to have a transdermal gel option available on the PBS to manage this condition.
- 6.4 The clinician stated that evidence showed that MP did not significantly increase the risk of breast cancer, unlike synthetic progestogens which showed an increased breast cancer risk after 5 years of use. The clinician further stated that international guidelines support the safety aspect of MP over synthetic progestogens. The clinician stated MP also has the secondary benefits of mood stabilisation and benefits on sleep quality for some patients.

Estradiol

Consumer comments

- 6.5 The PBAC noted and welcomed the input from individuals (108), health care professionals (8) and organisations (4 – Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG); Women’s Health & Research Institute of Australia; Inherited Cancers Australia; SPHERE Centre for Research Excellence, Monash University) via the Consumer Comments facility on the PBS website. Health

professionals stated that Estrogel is a first-line treatment in particular situations, is evidence-based, has fewer adverse effects and risks compared to oral forms of estrogen (especially for patients with risk factors for VTE or cardiovascular disease), and that estrogen patches are not always tolerated.

6.6 The PBAC also noted input that:

- MHT patches are often not available due to shortages and have disadvantages such as falling off, and Estrogel is an alternative;
- while an estradiol gel product is available on the PBS, it is harder to use and adjust dosage compared to the Estrogel pump pack where the dose can be easily adjusted and individualised for the patient.
- the cost of Estrogel is a barrier to access and leads to equity issues.

6.7 Consumers stated benefits of using Estrogel, including improvements in hot flushes, mood, brain fog, migraine, anxiety, insomnia, aches and pains, hair loss, balancing hormonal fluctuations, and protection against heart conditions and bone density loss.

6.8 Consumers commented on challenges with using other MHT products, including oral MHT products being ineffective and leading to adverse effects, allergy to excipients in patches, and being unable to use oral estradiol due to comorbidities. Adverse effects associated with Estrogel included larger breasts and low-grade thrush.

6.9 Consumers commented using this medicine allowed them to more fully participate in work and everyday activities, have improved quality of life, and keep healthy relationships.

6.10 SPHERE Centre for Research Excellence, Monash University, commented that that estradiol is an effective option for hot flushes in particular, and is also an effective option for managing other perimenopause and menopause symptoms such as night sweats, vaginal dryness, itchiness and dysuria. It further stated that topical estrogen is considered the safest delivery method due to the reduced risk of VTE compared to oral preparations. Estradiol has potential benefits on mood, cardiovascular health and protecting bone health and reducing the risk of osteoporosis.

6.11 The Women's Health & Research Institute of Australia discussed the advantages of topical as opposed to oral estrogens, and oral estradiol being safer for women at risk of thrombosis. It noted that women who are obese, have a clotting disorder (or a past history of a clot) should avoid oral estradiol and use estradiol patches or gel. It also noted many women were intolerant to the adhesive in patches and also expressed concern at the shortage of supply of patches.

Clinical trials

6.12 No head-to-head trial comparing Estrogel to Sandrena was available. The submission identified two placebo-controlled trials: one for Estrogel (CV141-001), reported by Archer et al., 2003 and Archer et al., 2012, and one for Sandrena, reported by Hedrick

et al., 2009 and Hedrick et al., 2010. The data required for a formal indirect treatment comparison (ITC) of efficacy were not available for the Sandrena trial, resulting in the submission being based on a side-by-side comparison of Estrogel and Sandrena. However, an ITC of treatment-related adverse events (AEs) between the two trials was presented. The ESC noted the two trials provided were relatively small studies, and the study duration was 12 weeks, which does not provide long term data.

6.13 Details of the trials presented in the submission are provided in Table 4.

Table 4: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CV141-001	Efficacy and safety comparison of Estrogel Gel (17β-estradiol in a topical gel) and placebo gel in the treatment of menopausal women with vasomotor symptoms.	30 June 1999
	Archer D, and E. S. Group, Percutaneous 17β-estradiol gel for the treatment of vasomotor symptoms in postmenopausal women.	Menopause 2003; 10(6): 516-21.
	Archer D, Pickar J, et al. Transdermal estradiol gel for the treatment of symptomatic postmenopausal women.	Menopause 2012; 19(6): 622-9.
Sandrena Trial	Hedrick R, Ackerman R, et al. Transdermal estradiol gel 0.1% for the treatment of vasomotor symptoms in postmenopausal women.	Menopause 2009; 16(1): 132-40.
	Hedrick R, Ackerman R, et al. Estradiol gel 0.1% relieves vasomotor symptoms independent of age, ovarian status, or uterine status.	Menopause 2010; 17(6): 1167-73.

Source: Table 2.3, p56 of the submission main body.

6.14 The key features of the included evidence are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Estrogel versus placebo					
CV141-001 (Archer et al., 2003)	221; 1.25 g=75 2.5 g=73 PBO=73	Phase III, R, DB, PC Mean duration of treatment (SD): 11.4 weeks (2.35)	Low to moderate	Women with natural perimenopause or natural menopause (amenorrhea ≥6 months) or surgical amenorrhea (in women ≥45 years with hysterectomy with bilateral oophorectomy and serum estradiol ≤20 pg/mL and serum FSH ≥40 mIU/mL) and ≥7 moderate-to-severe hot flushes per day or ≥60 moderate-to-severe hot flushes per week.	Primary: change in frequency of moderate-to-severe hot flushes from baseline to 12 weeks Secondary: change in frequency of all hot flushes, change in severity of hot flushes, change in other estrogen-specific symptoms (vaginal bleeding and sleep disturbances) and maintenance of vaginal epithelium. Safety outcomes included the incidence of breast pain during treatment, incidence of treatment emergent signs and symptoms.
Sandrena versus placebo					
Sandrena trial (Hedrick et al., 2009)	N=495; 0.25 g=122 0.5 g=123 1.0 g=125 PBO=125	Phase III, R, DB, PC Mean duration: NR	Low to moderate	Women 18 years or older, with natural perimenopause (amenorrhea 6-12 months and serum estradiol <20 pg/mL and serum FSH ≥40 mIU/mL) or natural menopause (amenorrhea	Co-primary endpoints: change in frequency and severity of moderate-to-severe hot flushes from baseline to Week 4 and 12 weeks. Secondary: change in the signs of vaginal and vulvar atrophy.

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
				≥12 months), surgical menopause (≥6 weeks postsurgical bilateral oophorectomy with or without hysterectomy or post-hysterectomy with or without oophorectomy), and 50 moderate-to-severe hot flushes per week.	Safety outcomes included monitoring of adverse events, blood parameters, breast and gynaecological examination and skin tolerability.

Source: Table 2.6, p61; Table 2.7, p63; Table 2.8, p64; Table 2.14, pp68-69; and Table 2.15, p70 of the submission main body.

DB = double blind; FSH = follicle-stimulating hormone; N = total participants in group; NR = not reported; PBO = placebo; PC = placebo-controlled; R = randomised; SD = standard deviation.

- 6.15 A claim of non-inferiority for Estrogel (2.5 g and 1.5 g) over Sandrena (1.0 g and 0.5 g) was based on the efficacy outcomes of reducing the frequency of moderate to severe hot flushes and safety outcomes of AE and treatment-related AEs (TRAE). Furthermore, the submission claimed that Estrogel offers the additional benefit of preventing osteoporosis in postmenopausal women at high risk of future fractures, compared to Sandrena. However, no evidence was presented to support this claim of preventing osteoporosis.
- 6.16 The PSCR stated that a conservative approach was applied in the submission by not modelling this additional clinical benefit, but noted that Sandrena does not have the same TGA-registered indication of preventing osteoporosis in postmenopausal women at high risk of future fractures. It cited three company-sponsored studies and eight non-company sponsored studies, which are referred to in the Product Information for Estrogel for efficacy data, which found that bone mineral content and density remained stable or increased while using Estrogel (3 mg estradiol) but decreased when using placebo. One study found no change in bone mineral density with either Estrogel or placebo, however the study was of a shorter duration (1 year vs 2 years) and used a lower dose of Estrogel (0.75-1.5 mg/day).
- 6.17 The submission did not propose a non-inferiority margin. The absence of a non-inferiority margin makes it difficult to assess the non-inferiority claim with certainty.

Comparative effectiveness

- 6.18 The submission presented comparisons at the higher dose of Estrogel 2.5 g versus Sandrena 1.0 g and at the lower dose of Estrogel 1.25 g and Sandrena 0.5 g.
- 6.19 Table 6 summarises the change in frequency of moderate-to-severe hot flushes (primary efficacy outcome) from baseline to Week 12 for both Estrogel and Sandrena.

Table 6: Results of change from baseline to week 12 in the frequency of moderate to severe hot flushes across the trials – Estrogel and Sandrena trials

Intervention	Estrogel Mean (SD)	Placebo (N=73) Mean (SD)	Difference in means (95% CI)	SE
Estrogel 1.25 g (N=75)	-7.8 (0.53)	-5.7 (0.52)	-2.1 (-2.27, -1.93)	0.086
Estrogel 2.5 g (N=73)	-8.5 (0.53)	-5.7 (0.52)	-2.8 (-2.97, -2.63)	0.087
Comparator	Sandrena Mean (SD)	Placebo (N=125) Mean (SD)	Difference in means (95% CI)	SE
Sandrena 0.5 g (N=119)	-7.5	-5.3	-2.2 (NR, NR)	NR
Sandrena 1.0 g (N=124)	-8.9	-5.3	-3.6 (NR, NR)	NR

Source: Table 2.28, p84; and Table 2.29, p85 of the submission main body.

CI = confidence interval; N= total participants in group; NR= not reported; SD = standard deviation; SE = standard error.

Bold indicates statistically significant change.

- 6.20 Estrogel demonstrated a significant reduction in the mean frequency of moderate-to-severe hot flushes from baseline to Week 12 compared to placebo.
- 6.21 Sandrena demonstrated a significant reduction in both the median and mean frequency of moderate-to-severe hot flushes from baseline to Week 12 compared to placebo.
- 6.22 For both Estrogel and Sandrena, higher doses were associated with greater reductions in moderate-to-severe hot flushes. Estrogel 2.5 g showed significant improvement from Week 5, while Estrogel 1.25 g was significant from Week 6 onwards. Sandrena 1.0 g and 0.5 g showed significant reductions from Week 4, with Sandrena 1.0 g showing significant improvement as early as Week 2. The PBAC noted that the time to reduce symptoms may be earlier with Sandrena, but this was uncertain.
- 6.23 The submission also presented the change in severity of hot flushes, which was a secondary outcome in the Estrogel trial and a primary co-endpoint in the Sandrena trial. Compared to placebo, Estrogel 2.5 g and 1.25 g showed significant reduction in mean change from baseline in the severity of hot flush from Week 2 (-0.6) and Week 6 (-0.8), respectively. Compared to placebo, Sandrena 1.0 g and 0.5 g also showed significant reductions in median severity of hot flushes from baseline starting at Week 2 (-0.12) and Week 3 (-0.10), respectively, with these improvements maintained throughout the treatment period.

Comparative harms

- 6.24 In the Estrogel trial, the most common treatment-emergent adverse events (TEAEs) in ≥5% of women included headache (18%), breast pain (10%), infection (10%), pain (8%), nausea (7%), rash (5%), and vaginitis (5%), with higher incidences in the Estrogel 2.5 g group compared to those using Estrogel 1.25 g. Estrogel 2.5 g (19%) had a higher incidence of estrogen-specific TEAEs than Estrogel 1.25 g (17%) and placebo (18%), although not statistically significant. Breast pain was similar across Estrogel groups (11%) and placebo (10%). Metrorrhagia was significantly higher with Estrogel 2.5 g (7%) compared to placebo (0%).

- 6.25 In the Sandrena trial, the most common TEAEs in $\geq 5\%$ of women were postmenopausal bleeding (8%) and breast tenderness (7%), vaginal mycosis (4%), nasopharyngitis (4%), and upper respiratory tract infection (2%), with higher incidences observed in the Sandrena 1.0 g group compared to 0.5 g group.
- 6.26 A higher proportion of patients reported TRAEs in the EstroGel trial (36% of all women) compared to the Sandrena trial (21% of all women). In the EstroGel trial, incidences were higher in EstroGel 2.5 g compared to EstroGel 1.5 g (45% versus 34%). Among the Sandrena trial, the incidence was higher with Sandrena 1 g compared to Sandrena 0.5 g (34% versus 21%). The PBAC noted the higher proportion of patients reporting adverse effects with EstroGel compared to Sandrena.
- 6.27 Discontinuations due to AEs or serious AEs was low across both trials. Treatment with EstroGel 2.5 g and Sandrena 1 g was associated with slightly more discontinuations compared to EstroGel 1.25 g (4% versus 3%) and Sandrena 0.5 g (5% versus 1%). No deaths were reported in the EstroGel trial, while data was not available for Sandrena.
- 6.28 The results of the ITC of safety in terms of TRAEs between the lower and higher effective doses of EstroGel and Sandrena is summarised in Table 7.

Table 7: Results of the indirect comparison for treatment related adverse events

Treatment and strength	Treatment group n/N (%)	Placebo n/N (%)	Odds ratio (95% CL)	Relative Risk (95% CL)	Risk Difference (95% CL)
EstroGel 1.25 g	26/75 (34.7%)	22/73 (30.1%)	1.23 (0.62, 2.45)	1.15 (0.72, 1.84)	0.05 (-0.11, 0.20)
EstroGel 2.5 g	33/73 (45.2%)	22/73 (30.1%)	1.91 (0.97, 3.78)	1.50 (0.98, 2.31)	0.15 (-0.005, 0.31)
Sandrena 0.5 g	26/123 (21.1%)	15/125 (12.0%)	2.0 (0.98, 3.93)	1.76 (0.98, 3.16)	0.09 (-0.001, 0.18)
Sandrena 1.0 g	43/125 (34.4%)	15/125 (12.0%)	3.85 (2.00, 7.39)	2.87 (1.68, 4.88)	0.22 (0.12, 0.33)
ITC of EstroGel 1.25 g vs. Sandrena 0.5 g			0.63 (0.24, 1.66)	0.65 (0.31, 1.38)	-0.046 (-0.22, 0.13)
ITC of EstroGel 2.5 g vs. Sandrena 1.0 g			0.50 (0.19, 1.28)	0.52 (0.26, 1.04)	-0.07 (-0.26, 0.11)

Source: Table 2.31, p86 and Table 2.32, p87 of the submission main body.

CL= confidence levels; ITC = indirect treatment comparison; n = number of participants reporting data; N = total participants in group.

- 6.29 Based on the ITC of safety in terms of TRAEs, EstroGel may be relatively safer than Sandrena; however, the results were not statistically significant. The submission stated whilst both EstroGel and Sandrena are both estradiol gels, there are some differences, including formulation, presentation and safety profile, that can impact clinical suitability and clinician and patient preference and may affect adherence (e.g. incidence of skin irritation associated with Sandrena).
- 6.30 The submission did not present any evidence regarding differences in itching or skin reactions between EstroGel and Sandrena. The pre-PBAC response claimed the Product Information for EstroGel and Sandrena suggest EstroGel is less likely to cause skin irritation compared to Sandrena gel, as it is listed as a 'common' adverse effect for Sandrena, but is not listed for EstroGel. The pre-PBAC response further claimed that propylene glycol, which is in Sandrena gel, is a common cause of irritant contact dermatitis and can cause contact urticaria and sensory irritation.
- 6.31 The ESC considered that EstroGel 1.25 g and 2.5 g has non-inferior safety compared to Sandrena 0.5 g and 1 g respectively.

Benefits/harms

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

Clinical claim

- 6.33 The submission described Estrogel as non-inferior in terms of effectiveness (reducing the frequency of moderate to severe hot flushes) compared to Sandrena. This claim was adequately supported; however, the submission did not provide any evidence supporting the claim that Estrogel provides additional benefit of preventing osteoporosis in postmenopausal women at high risk of future fractures.
- 6.34 The submission described Estrogel as non-inferior in terms of safety compared to Sandrena. This claim was adequately supported. No evidence was presented regarding differences in itching or skin reactions. The pre-PBAC response stated that reduction in skin irritation could be included in the clinical claim as an additional benefit of Estrogel compared to Sandrena, due to reasons cited in paragraph 6.30.
- 6.35 The ESC considered the claim that Estrogel has non-inferior efficacy (in reducing the frequency of moderate to severe hot flushes) compared to Sandrena was adequately supported by evidence. The PSCR claimed the submission took a conservative approach by not providing evidence or modelling the additional clinical benefit of preventing osteoporosis. The ESC noted findings from the Women's Health Initiative randomised trial (where women took conjugated equine estrogen 0.625 mg daily plus MPA 2.5 mg daily, or placebo) which found that 8.6% of women in the MHT group and 11.1% in the placebo group had a fracture, and total hip BMD increased 3.7% after 3 years of MHT compared with 0.14% in the placebo group.⁵
- 6.36 The ESC considered the claim that Estrogel has non-inferior safety compared to Sandrena was appropriate, but noted no evidence was provided on differences in itching or skin reactions.
- 6.37 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable.

Progesterone

Consumer comments

- 6.38 The PBAC noted and welcomed the input from individuals (59), health care professionals (7) and organisations (3 – RANZCOG; Women's Health & Research Institute of Australia; Inherited Cancers Australia) via the Consumer Comments facility on the PBS website. Health professionals stated that MHT products currently PBS-listed provide limited options, and listing Prometrium on the PBS would provide the

⁵ Cauley JA, Robbins J, Chen Z, et al, (2003), 'Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial', JAMA, 290, pp1729-38.

first body identical and best-practice progesterone, providing a better and safer subsidised option.

- 6.39 Consumers noted menopause has a range of symptoms (e.g. night sweats, muscle soreness, insomnia, hot flushes, itchy skin, memory loss) and impacts their quality of life, including having negative impacts on work, mental health (e.g. mood swings, depression, anxiety) and relationships, and MHT products can be difficult to obtain due to shortages. Health professionals and consumers commented that Prometrium reduces a range of menopause symptoms, including sleep disturbances, mood changes, joint pain, night sweats, bleeding, and leads to improved relationships and quality of life.
- 6.40 Comments stated that research has shown that Prometrium has fewer adverse effects and a lower breast cancer risk compared to progestins, and national and international menopause bodies agree the safest MHT is progesterone (with transdermal estrogen). Benefits cited with Prometrium included reduced cardiovascular and breast risks, effective endometrial protection, and that it would be beneficial to have a range of MHT options on the PBS.
- 6.41 Private market cost was noted as a barrier to access and caused equity issues. One comment suggested some patients may use less than the correct dose because of the cost.
- 6.42 The Women's Health & Research Institute of Australia stated that synthetic progestins are not tolerated by many women, negate the cardiovascular benefits of estrogen, and have a higher risk of breast cancer than Prometrium. It commented that Prometrium has fewer adverse effects, appears to have a lower risk of breast cancer and does not negate the cardiovascular benefits of estrogen. Prometrium can help maintain a balanced mood, healthy sex life and sleep patterns during and after menopause.

Clinical trials

- 6.43 The submission was based on five randomised trials of MP versus MPA and two observational studies comparing MP with MPA and norethisterone.
- 6.44 Evidence for the primary clinical claim that MP is comparable to MPA in protecting against the development of estrogen-associated endometrial hyperplasia was based on two direct randomised controlled trials (RCTs): PEPI trial/Judd et al., 1996 and Lorrain et al., 1994. Additionally, three direct RCTs (Mittal et al., 2020, Gao et al., 2018, and PEPI trial/Greendale et al., 1998) provided data on the comparative effectiveness of MP versus MPA in reducing menopausal symptoms.
- 6.45 The clinical claim for the primary safety outcome of breast cancer was based on within-study indirect comparisons from two observational studies: Yuk, 2024, and Abenhaim et al., 2022. Furthermore, three RCTs (Di Carlo et al., 2005, PEPI trial/Lindenfeld et al., 2002, and Lorrain et al., 1994) provided data on the impact of MP versus MPA on bleeding patterns, while three direct RCTs (Mittal et al., 2020, PEPI

trial/Greendale et al., 1998, and Lorrain et al., 1994) provided data on the AEs of adding MP versus MPA to estrogen therapy.

6.46 Details of the included evidence presented in the submission are provided in Table 8.

Table 8: Trials and studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
RCTs (MP versus MPA)		
Mittal 2020	Mittal M, Panay N, Supramaniam PR, et al. A direct comparison of women's perceptions and acceptability of micronised progesterone and medroxyprogesterone acetate in combination with transdermal oestradiol in the management of young postmenopausal women, under 45 years of age.	Post Reproductive Health 2020; 26(4): 210-9.
Gao 2018	Gao L, Zheng T, Xue W, et al. Efficacy and safety evaluation of Cimicifuga foetida extract in menopausal women.	Climacteric 2020; 21(1): 69-74.
Di Carlo 2005	Di Carlo C, Sammartino A, Di Spiezio Sardo A, et al. Bleeding patterns during continuous estradiol with different sequential progestogens therapy.	Menopause 2005; 12(5): 520-5.
PEPI trial/ Lindenfeld 2002	Lindenfeld EA, and Langer RD. Bleeding patterns of the hormone replacement therapies in the postmenopausal estrogen and progestin interventions trial.	Obstetrics and Gynaecology 2002; 100(5): 853-63.
PEPI trial/ Greendale 1998	Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: Results from the postmenopausal estrogen/progestin interventions trial.	Obstetrics and Gynaecology 1998; 92(6): 982-8.
PEPI trial/Judd 1996	Judd HL, Meoane-Sims I, Legault C, et al. Effects of hormone replacement therapy on endometrial histology in postmenopausal women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.	Journal of the American Medical Association 1996; 275(5): 370-5.
Lorrain 1994 CSR	Efficacy, safety and tolerance of Utrogestan® compared to medroxyprogesterone acetate in menopausal women receiving Estraderm®.	CSR. November 1994.
Observational studies (MP versus MPA or norethisterone)		
Yuk 2024	Yuk JS. Relationship between menopausal hormone therapy and breast cancer: A nationwide population-based cohort study.	International Journal of Gynaecology and Obstetrics 2024; 166(2): 735-44.
Abenhaim 2022	Abenhaim HA, Suissa S, Azoulay L, et al. Menopausal Hormone Therapy Formulation and Breast Cancer Risk.	Obstetrics and Gynaecology 2022; 139(6): 1103-10.

Source: Table 2.41, pp99-100 of the submission main body.

CSR = clinical study report; MP = micronised progesterone; MPA = medroxyprogesterone acetate; PEPI = Postmenopausal Estrogen/Progestin Interventions; RCT = randomised controlled trial.

6.47 The key features of the included evidence are summarised in Table 9.

Table 9: Key features of the included evidence

Trial	N	Design/ Follow-up duration	Risk of bias [#]	Patient population	Outcome(s)
RCTs (MP versus MPA)					
Mittal 2020	67	RCT, PC, OL 12 months	High	Young postmenopausal women aged <45 years	Menopausal symptoms, adverse effects
Gao 2018	96	RCT, PC, OL 24 months	High	Early menopausal women	Menopausal symptoms, Endometrial thickness [#]
Di Carlo 2005	100	RCT, PC, OL 12 cycles	High	Healthy women with at least 12 months and no more than 36 months post-menopause	Bleeding pattern
PEPI trial/ Lindenfeld 2002	596	RCT, PC, DB 3 years	Moderate	Postmenopausal women aged 45- 64 years with an intact uterus without contraindication to hormone therapy	Bleeding pattern
PEPI trial/ Greendale 1998	875	RCT, PC; DB 3 years	Moderate	Postmenopausal women aged 45-64 years without contraindication to hormone therapy	Menopausal symptoms [#] , adverse effects [#]
PEPI trial/Judd 1996	596	RCT, PC, DB 3 years	Moderate	Postmenopausal women aged 45- 64 years with an intact uterus without contraindication to hormone therapy	Endometrial hyperplasia
Lorrain 1994 CSR	40	RCT, PC, OL At least 13 cycles	High	Healthy postmenopausal women of any age with a uterus who required HRT for menopausal symptoms	Endometrial hyperplasia, bleeding pattern, adverse effects
Observational studies (MP versus MPA or norethisterone)					
Yuk 2024	307,472	Retrospective population-based cohort (2011-2014) median 7.9 years	High	Women aged >40 years	Risk of breast cancer
Abenheim 2022	475,013	Population-based case-control; 1995- 2014	High	Women aged ≥50 years	Risk of breast cancer

Source: Table 2.55, p119; Table 2.57, p121; Table 2.62, p127; Table 2.65, p131; Table 2.70, p133 of the submission main body.

CSR = Clinical Study Report; DB = double blind; HRT = hormone replacement therapy; OL = open label; MP = micronised progesterone; MPA = medroxyprogesterone acetate; N = number of total participants; PC = placebo-controlled; PEPI = Postmenopausal Estrogen/Progestin Interventions trial; RCT = randomised controlled trial.

[#]added during evaluation.

6.48 Different estrogens (CEE: conjugated equine estrogen; E2: transdermal estradiol; EV: estradiol valerate) and varying regimens (cyclical and continuous) were used with MP and MPA across the trials; details of the treatment protocols for each trial are presented in the table below.

Table 10: Interventions compared across the randomised trials

Treatment	Dosage regimen	Duration of treatment (months)
Mittal 2020		
E2 + MP (cyclical)	E2: transdermal 17b-estradiol 50 µg/day (28-day cycle) MP: oral 200 mg/day on days 15-26 (28-day cycle)	12 months
E2 + MPA (cyclical)	E2: transdermal 17b-estradiol 50 µg/day (28-day cycle) MPA: oral 10 mg/day on days 16-26 (28-day cycle)	
Gao 2018		
EV + MP (cyclical)	EV: oral 1 mg/day for 30 days MP: oral 100 mg/day on days 19-30	24 months
EV + MPA (cyclical)	EV: oral 1 mg/day for 30 days MPA: oral 4 mg/day on days 19-30	
Di Carlo 2005		
E2 + MP (cyclical)	E2: transdermal 17b-estradiol 50 µg/day for 28 days MP: oral 200 mg/day on days 14-25	~11 months [#] (12 cycles)
E2 + MPA (cyclical)	E2: transdermal 17b-estradiol 50 µg/day for 28 days MPA: oral 10 mg/day on days 14-25	
PEPI Trial (Judd 1996; Greendale 1998; and Lindendorf 2002)		
CEE + MP (cyclical)	CEE: oral 0.625 mg/day for 28 days MP: oral 200 mg/day on days 1-12	36 months (3 years)
CEE + MPA (cyclical)	CEE: oral 0.625 mg/day for 28 days MPA: oral 10 mg/day on days 1-12	
CEE + MPA (continuous)	CEE: oral 0.625 mg/day for 28 days MPA: oral 2.5 mg/day for 28 days	
Lorrain 1994		
E2 + MP (cyclical)	E2: transdermal 17b-estradiol 50 µg/day for 25 days (28-day cycle) MP: oral 200 mg/day on days 14-25 (28-day cycle)	~12 months [#] (13 cycles)
E2 + MPA (cyclical)	E2: transdermal 17b-estradiol 50 µg/day for 25 days (28-day cycle) MPA: oral 10 mg/day on days 14-25 (28-day cycle)	

Source: Table 2.52, p111 and Section 2.2.4.1.3, p110 of the submission main body.

CEE = conjugated equine estrogen; E2 = estradiol; EV = estradiol valerate; MP = micronised progesterone; MPA = medroxyprogesterone acetate; PEPI = Postmenopausal Estrogen/Progestin Interventions.

[#]corrected during evaluation.

Note: Treatment arms not relevant to the current submission were not presented.

6.49 The submission requested listings for both the cyclic MP regimen of 200 mg/day for 12 days in the last half of each therapeutic cycle (starting on day 15 and ending on day 26) and the continuous MP regimen of 100 mg/day from day 1 to day 25 of each cycle. However, all trials included in the submission were based exclusively on the cyclic MP regimen. Based on the Australasian Menopause Society information sheet⁶, cyclic MHT is typically used for perimenopausal women or those in menopause transition, whereas continuous MHT is used for postmenopausal women. Consequently, there may be applicability issues, as no trial data were presented for the continuous MP regimen used in clinical practice for postmenopausal women.

⁶Australasian Menopause Society, (2023), 'AMS Guide to MHT/HRT doses Australia only', available at www.menopause.org.au/hp/information-sheets/ams-guide-to-mht-hrt-doses

- 6.50 The dosing regimen of MP and MPA in all trials aligned with the recommended dosing in the respective Product Information, except in Gao et al. (2018), where participants received only half of the recommended dose.
- 6.51 Yuk (2024) compared MHT regimens using specific estrogen/progesterone combinations against no MHT, while Abenheim et al. (2022) evaluated various estrogen types (bioidentical, animal-derived, or both) and progestogen types (bioidentical, animal-derived, or both) against no treatment. However, neither of these observational studies provided specific details on dosing or whether the regimens were cyclical or continuous.

Comparative effectiveness

Endometrial hyperplasia (primary efficacy outcome)

- 6.52 Table 11 summarises the results of the impact of MHT on endometrial hyperplasia from the PEPI trial reported by Judd et al., 1996.

Table 11: Results of the impact of MHT on endometrial hyperplasia: overall and by increasing severity – PEPI trial

Proposed medicine n/N (%)		Main comparator n/N (%)		RR (95% CI) ^a	RD (95% CI) ^a
Overall					
CEE + MP# (cyc)	6/120 (5.0)	CEE + MPA (cyc)	6/118 (5.1)	0.98 (0.33, 2.96)	-0.00 (-0.06, 0.05)
CEE + MP (cyc)	6/120 (5.0)	CEE + MPA (cont)	1/120 (0.8)	6.00 (0.73, 49.1)	0.04 (-0.00, 0.08)
Simple (cystic) hyperplasia					
CEE + MP (cyc)	5/120 (4.2)	CEE + MPA (cyc)	4/118 (3.4)	1.23 (0.34, 4.47)	0.01 (-0.04, 0.06)
CEE + MP (cyc)	5/120 (4.2)	CEE + MPA (cont)	1/120 (0.8)	5.00 (0.59, 42.2)	0.03 (-0.01, 0.07)
Complex (adenomatous) hyperplasia					
CEE + MP (cyc)	0/120 (0)	CEE + MPA (cyc)	2/118 (1.7)	0.20 (0.01, 4.05)	-0.02 (-0.05, 0.01)
CEE + MP (cyc)	0/120 (0)	CEE + MPA (cont)	0/120 (0)	NE	NE
Atypia					
CEE + MP (cyc)	1/120 (8.3)	CEE + MPA (cyc)	0/118 (0)	2.95 (0.12, 71.7)	0.01 (-0.01, 0.03)
CEE + MP (cyc)	1/120 (8.3)	CEE + MPA (cont)	0/120 (0)	3.00 (0.12, 72.9)	0.01 (-0.01, 0.03)
Adenocarcinoma					
CEE + MP (cyc)	0/120 (0)	CEE + MPA (cyc)	0/118 (0)	NE	NE
CEE + MP (cyc)	0/120 (0)	CEE + MPA (cont)	0/120 (0)	NE	NE

Source: Table 2.56, p120 of the submission main body.

CEE = conjugated equine estrogen; CI = confidence interval; cont = continuous; cyc = cyclical; MHT = menopause hormone therapy; MP = micronised progesterone; MPA = medroxyprogesterone acetate; n = number of participants with event; N = total participants in group; NE = not evaluable; PEPI = Postmenopausal Estrogen/Progestin Interventions; RD = risk difference; RR = relative risk.

#corrected during evaluation.

^a Post hoc analyses were conducted by the submission using RevMan 5.0.

Note: Only treatments relevant to the submission were presented.

- 6.53 There was no statistically significant difference in the risk of endometrial changes (e.g., simple/complex hyperplasia, atypia) between cyclic MP and cyclic MPA or continuous MPA. However, continuous MPA appeared to be slightly more protective than both cyclic MP and cyclic MPA, with only 1/120 patients developing endometrial hyperplasia in the CEE + MPA (continuous) arm compared with 6/118 in the CEE + MPA (cyclical) arm and 6/120 in CEE + MP (cyclical) arm. This further supports the guidelines recommendations for continuous combined MHT for postmenopausal women.

- 6.54 Lorrain et al. (1994) reported three cases of endometrial hyperplasia in the MP arm, compared to none in the MPA arm; however, those cases were not confirmed by a central pathologist. No significant anomalies were detected in the biopsies for either treatment arm, and MP and MPA appeared comparable during at least the first two years.
- 6.55 Notably, the submission did not present results from Gao et al., 2018 for endometrial thickness. At 12 months, the mean endometrial thickness remained relatively stable compared to baseline in the EV + MPA arm but increased by 28% in the EV + MP arm, although this change was not statistically significant. Additionally, the EV + MP arm had 12 more patients with endometrial thickness ≥ 5 mm compared to baseline, while the EV + MPA arm had five more patients.

Menopausal symptoms

- 6.56 According to Mittal et al., 2020, at baseline, the most commonly reported symptoms in both MP and MPA arms were low energy levels (44.8%), VMS (hot flushes; 41.8%) and sexual dysfunction (low libido; 26.9%). A comparison of the reported symptoms between the E2 + MP and E2 + MPA over the course of the study demonstrated no significant difference, except for vaginal dryness which was found to be more prevalent within the E2 + MP arm compared to the E2 + MPA arm at 3-months duration, but this difference was not maintained by 12-months duration.
- 6.57 According to Gao et al. (2018), both EV + MP and EV + MPA showed significant reductions in Kupperman Menopausal Index (mKMI) scores following treatment. Anxiety scores decreased significantly after 9 months with EV + MPA and 3 months with EV + MP. Depression scores also decreased significantly, with reductions observed after 9 months with EV + MPA and 15 months with EV + MP. Furthermore, scores for the vasomotor, psychosocial, and physical domains of the MENQOL questionnaire decreased similarly after treatment in both the EV + MP and EV + MPA arms. However, the sexual domain score did not change significantly from baseline in the EV + MP arm, while it showed a significant improvement in the EV + MPA arm.
- 6.58 According to Greendale et al., (1998), compared to CEE + MP (cyclical), there was no significant difference of having higher VMS with CEE + MPA (cyclical; OR = 1.09; 95% CI: 0.58, 2.06) or CEE + MPA (continuous; OR = 0.81; 95% CI 0.41, 1.60). At Year 2, although the difference was not statistically significant, the CEE + MPA (cyclical and continuous) arms tended to have higher odds compared to the CEE + MP arm.
- 6.59 Overall, results from Mittal et al., 2020, Gao et al., 2018, and the PEPI trial (Greendale et al., 1998) suggested that adding cyclical MP to estrogen therapy did not negatively impact its effectiveness in managing menopausal symptoms compared to cyclical or continuous MPA.
- 6.60 The ESC noted that the results from the studies on the effect of MP on menopausal symptoms varied, from no change in energy levels, vasomotor symptoms or sexual

dysfunction (Mittal et al., 2020), to overall reductions in Kupperman Menopausal Index scores and improved mental health (Gao et al., 2018).

Comparative harms

Risk of breast cancer (primary safety outcome)

- 6.61 To inform the relative safety of MP versus MPA, the submission utilised data from Yuk (2024) to conduct a post hoc within-study ITC, using MHT as common comparator, with or without controlling for the estrogen type (i.e., similar estrogen or any type of estrogen).
- 6.62 Table 12 summarises the impact of MHT on breast cancer risk as reported by Yuk (2024), including the post hoc within-study ITC conducted in the submission.

Table 12: Results of the impact of MHT on breast cancer risk – Yuk (2024)

MHT type	No breast cancer cases n (%)	Breast cancer cases n (%)	Breast cancer cases/100 000 person-years	HR (95% CI) vs no MHT
CEE-based				
CEE + MP (PC) vs no MHT	424 (99.8)	1 (0.2)	1/2,905 (34)	0.22 (0.03, 1.58)
CEE + MPA (PC) vs no MHT	111 (98.2)	2 (1.8)	2/659 (303)	2.01 (0.5, 8.02)
ITC MP (PC) vs MPA (PC)#				0.11 (0.01, 1.23)
EV-based				
EV + MP (PC) vs no MHT	452 (99.1)	4 (0.9)	4/3,259 (123)	0.79 (0.3, 2.11)
EV + MPA (PC) vs no MHT	304 (97.7)	7 (2.3)	7/2,188 (320)	2.07 (0.98, 4.34)
ITC MP (PC) vs MPA (PC)#				0.38 (0.11, 1.30)
EV + MP (PC) vs no MHT	452 (99.1)	4 (0.9)	4/3,259 (123)	0.79 (0.3, 2.11)
EV + MPA (MC) vs no MHT	930 (98.2)	17 (1.8)	17/7,141 (238)	1.53 (0.95, 2.46)
ITC MP (PC) vs MPA (MC)#				0.52 (0.17, 1.53)
EV + MP (PC) vs no MHT	452 (99.1)	4 (0.9)	4/3,259 (123)	0.79 (0.3, 2.11)
EV + NETA (MC) vs no MHT	135 (97.8)	3 (2.2)	3/1,079 (278)	1.77 (0.57, 5.50)
ITC MP (PC) vs NETA (MC)#				0.45 (0.10, 1.99)
EH-based				
EH + MP (PC) vs no MHT	229 (99.1)	2 (0.9)	2/1,686 (119)	0.76 (0.19, 3.05)
EH + NETA (MC) vs no MHT	4,452 (98.1)	87 (1.9)	87/33,573 (259)	1.66 (1.34, 2.06)
ITC MP (PC) vs NETA (MC)#				0.46 (0.11, 1.87)
Any E-based				
Any E + MP (PC) vs no MHT				0.49 (0.23, 1.02)
Any E + MPA (PC or MC) vs no MHT				1.45 (0.98, 2.14)
ITC MP (PC) vs MPA (PC or MC)#				0.33 (0.15, 0.77)
Any E + MP (PC) vs no MHT				0.49 (0.23, 1.02)
Any E + NETA (PC or MC) vs no MHT				1.48 (1.20, 1.82)
ITC MP (PC) vs NETA (PC or MC)#				0.33 (0.15, 0.71)

Source: Table 2.78, p146 of the submission main body.

CEE = conjugated equine estrogen; CI = confidence interval; E-based = estradiol-based; EH = estradiol hemihydrate; EV = estradiol valerate; HR = hazard ratio; ITC = indirect treatment comparison; MHT = menopause hormone therapy; MC = manufacturer; MP = micronised progesterone; MPA = medroxyprogesterone acetate; n = number of participants reporting data; N = total participants in group; NETA = norethisterone acetate; PC = physician.

Bold indicates statistical significance.

#calculated post hoc within-study ITC by the submission.

Note: Participants' propensity score matched on age, follow-up period, calendar year at inclusion, age at inclusion, socioeconomic status, region, Charlson Comorbidity Index, hypertension, diabetes mellitus, dyslipidaemia, uterine fibroids, endometriosis, previous hysterectomy and previous adnexal surgery.

Only treatments relevant to the submission were presented.

- 6.63 Yuk (2024) reported that MP showed a non-significant trend towards lower breast cancer risk compared to the non-MHT group. In contrast, MPA and norethisterone were associated with a trend towards higher breast cancer risk compared to non-MHT users. Specifically, the number of breast cancer cases per 100,000 person-years was 34 for CEE + MP (versus 128 for CEE alone), 123 for EV + MP (versus 163 for EV alone), and 119 for EH + MP (versus 178 for EH alone). Additionally, that study indicated that the risk of breast cancer increased with prolonged MHT use.
- 6.64 The post hoc within-study ITC, using no MHT as a common comparator and any type of estrogen, showed that the risk of breast cancer was significantly lower for MP compared with MPA (hazard ratio [HR] = 0.33; 95% CI: 0.15, 0.71) and norethisterone (HR = 0.33; 95% CI: 0.15, 0.77). The post hoc within-study ITC, using no MHT as a

common comparator and similar estrogens, demonstrated a consistently lower risk of breast cancer for MP compared to MPA and norethisterone. Although these differences did not reach statistical significance due to limited power, all HRs were substantially below 1, indicating a potentially lower risk of breast cancer with MP.

6.65 Table 13 summarises the impact of MHT on breast cancer risk as reported by Abenhaim (2022).

Table 13: Results of the impact of MHT on breast cancer risk – Abenhaim (2022)

Type of hormone	Control group n (%)	Case group n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Women aged ≥50 years				
N	431,830	43,183	-	-
Progestogen ^a				
No progestogen	410,256 (95.0)	40,352 (93.4)	1.0 (Ref)	1.0 (Ref)
Bioidentical (MP)	125 (0.03)	12 (0.03)	0.98 (0.54, 1.77)	0.99 (0.55, 1.79)
Synthetic	21,434 (5.0)	2,817 (6.5)	1.34 (1.28, 1.39)	1.28 (1.22, 1.35)
Women aged 50-60 years				
N	143,070	14,307	-	-
Progestogen ^a				
No progestogen	133,049 (93.0)	13,162 (92.0)	1.0 (Ref)	1.0 (Ref)
Bioidentical (MP)	72 (0.1)	10 (0.1)	0.98 (0.54, 1.77)	0.98 (0.54, 1.77)
Synthetic	9,941 (7.0)	1,134 (7.9)	1.34 (1.28, 1.39)	1.28 (1.21, 1.34)

Source: Table 2.64, p130 of the submission main body.

CI = confidence interval; MHT = menopause hormone therapy; MP = micronised progesterone; n = number of participants reporting data; N = total participants in group; OR = odds ratio.

Bold indicates statistical significance.

^a Adjusted for exposure to estrogen therapy and age, body mass index, smoking status, alcohol consumption, hysterectomy, oophorectomy, history of endometrial cancer, history of family breast cancer, and oral contraceptive use.

Only treatments relevant to the submission were presented.

6.66 According to Abenhaim et al., 2022, MP was not associated with an increased risk of breast cancer compared to no progestogen treatment (HR 0.98; 95% CI 0.54, 1.77). In contrast, synthetic progestogens (e.g., MPA) were associated with an increased risk (HR = 1.28; 95% CI 1.21, 1.34). The study concluded that the increased risk of breast cancer associated with MHT is mainly linked to synthetic progestins, suggesting that MP may be a safer alternative.

6.67 Similar to Yuk (2024), the submission used data from the UK study by Abenhaim et al., 2022 to perform a post hoc within-study ITC with no progestogen as the common comparator. This analysis found no significant difference in breast cancer risk between MP and MPA. However, the odds ratio for MP compared to MPA was less than 1 (0.77; 95% CI: 0.43, 1.40).

6.68 Both Yuk (2024) and Abenhaim et al. (2022) indicated that MP might be associated with a lower risk of breast cancer compared to MPA and norethisterone. However, the following uncertainties should be considered:

- The observational nature of the included studies and the post hoc within-study ITC conducted by the submission to estimate the relative effect of MP versus MPA.
- Yuk (2024) did not provide detailed information on the regimens' dosing or whether they were cyclical or continuous. Additionally, the study did not adjust

for key factors such as body mass index (BMI), parity, smoking, alcohol consumption, physical activity, or family history of breast cancer. Moreover, given that the study was conducted in South Korea (predominantly Asian population), its findings may not be directly applicable to the Australian population. The PSCR claimed that neither the Yuk nor Abenhaim study provided detailed information on the dosing regimens or whether they were cyclical or continuous. It claimed that as the data in the Yuk study was more recent (2011-2020) compared to that included in the Abenhaim study (1995-2014), the timing and dosing of the treatment regimens are likely to be more similar to dosing used in Australia, and claimed their findings are therefore more applicable to the Australian setting. The pre-PBAC response stated that publication of the initial findings from the Women's Health Initiative hormone therapy study occurred in 2002 which led to changes in the way MHT was used, and the use of MHT in the Abenhaim study is unlikely to reflect modern treatment practice. The pre-PBAC response reiterated the claim that the Yuk study is more applicable to the Australian setting as the data is more recent.

- Based on the results of the post hoc within-study ITC, a notable discrepancy was observed in the reported breast cancer risk reduction, with a HR of 0.33 (95% CI: 0.15, 0.71) in Yuk (2024) compared to an OR of 0.77 (95% CI: 0.43, 1.40) in Abenhaim et al., 2022. The reduction in breast cancer rates with MP may be overestimated in Yuk (2024) compared to Abenhaim et al., 2022. The PSCR claimed that this discrepancy was not unexpected for a number of reasons, including: data available for the Yuk study is more recent than that available for the Abenhaim study (2011 to 2020 versus 1995 to 2014) meaning that there may be some differences in the populations and how MHT was utilised between the two studies; the Yuk study was a retrospective cohort study with propensity score matching of exposure groups on potential confounding variables, while the Abenhaim study was a nested case-control study with adjustment of the analyses for potential confounding variables; risk in the Yuk study was analysed based on the incidence of breast cancer cases per 100,000 person-years (thus, a time-based component is included) while in the Abenhaim study it was analysed based on percentages (with no time-based component); hazard ratios (as used in the Yuk study) differ from ORs in that ORs are cumulative over an entire study, using a defined endpoint, while HRs represent instantaneous risk over the study time-period.
- Abenhaim et al., 2022 may provide more accurate and applicable results to the Australian context than Yuk (2024) as it was conducted in the UK and adjusted for important breast cancer risk factors such as age, BMI, smoking status, alcohol consumption, hysterectomy, oophorectomy, history of endometrial cancer, family history of breast cancer, and oral contraceptive use. The PSCR claimed that age and hysterectomy were included as propensity score matching variables in the Yuk study; in addition, in the Yuk study hypertension, diabetes mellitus and dyslipidemia are morbidities associated with a high BMI, and smoking and alcohol

consumption were also included, and these risk factors are therefore addressed in the Yuk study as well. The PSCR acknowledged that history of endometrial cancer, family history of breast cancer and oral contraceptive use were not included as variables in the Yuk study, however stated that variables such as socioeconomic status, region and Charlson Comorbidity Index were also not included as variables in the Abenheim study.

- 6.69 The PSCR further argued that the manner in which the Yuk study was conducted, with matching of the populations prior to analysis and the individual risks for each matched arm calculated as an incidence rate of breast cancer cases per 100,000 person-years, meant that this was the most appropriate data to inform the economic evaluation. The PSCR maintained that while the UK population may be considered to be more relevant to the Australian population compared to a study conducted in South Korea, based on the times when the two studies were conducted and the more recent Yuk study likely representing the treatment regimens used in Australia, using findings from the Yuk study is reasonable. The ESC noted that the population in the Abenheim study was likely more applicable to the Australian population (paragraph 6.82).

Adverse effects

- 6.70 Based on results from Di Carlo et al., 2005, there was a slightly lower incidence of regular bleeding with MP (64%) compared to MPA (72%). Conversely, MP was associated with a slightly higher incidence of irregular bleeding (12% versus 8%) and spotting (16% versus 10%) compared to MPA.
- 6.71 According to the PEPI trial, women on continuous CEE + MPA experienced bleeding on average for 99 days, about 9% of the treatment time. Among the two cyclical treatments, CEE + MP had lower cumulative bleeding compared to CEE + MPA: 23% fewer pads used, 23% fewer bleeding days, and 12% fewer bleeding episodes.
- 6.72 According to Lorrain et al., 1994, the incidence of amenorrheic cycles was higher in women treated with MP (19.5%) compared to those on MPA (3.4%). Breakthrough bleeding (spotting/light/important) was similar between MP (7/222, 3.2%) and MPA (8/181, 4.4%). Additionally, menstruation in women treated with MP occurred earlier, was less abundant, and had a shorter duration compared to those treated with MPA.
- 6.73 Based on results from Mittal et al., 2020, the proportion of respondents reporting adverse effects decreased from 73.9% at 3 months to 57.9% at 12 months in the E2 + MP treatment arm, though this change was not significant. Conversely, in the E2 + MPA arm, adverse effects increased from 76.9% at 3 months to 87.5% at 12 months, also not statistically significant.
- 6.74 No significant difference was observed between CEE + MP (cyclical; OR = 0.97; 95% CI: 0.63, 1.35) and CEE + MPA (cyclical or continuous; OR = 0.83; 95% CI: 0.53, 1.26) in the PEPI trial.

- 6.75 In terms of supportive safety outcomes, MP exhibited no significant negative impact on estrogen's effectiveness in reducing menopausal symptoms compared to MPA and demonstrated a similar safety profile with respect to bleeding and adverse effects.

Benefits/harms

- 6.76 A benefits and harms table is not presented as the submission made a claim of non-inferiority in terms of efficacy and safety, except for superiority in reduction of progestogen-associated breast cancer risk.
- 6.77 On the basis of direct evidence presented by the submission, for every 1,000 patients treated with MP in comparison with MPA over a median duration of follow-up of 7.9 years, approximately 2 fewer patients would have breast cancer.

Clinical claim

- 6.78 The submission described MP as non-inferior in terms of protecting against the development of estrogen-associated endometrial hyperplasia in menopausal women with an intact uterus receiving combination MHT compared with MPA. This claim was adequately supported.
- 6.79 The submission described MP as non-inferior in terms of preserving the effectiveness of estrogen at treating menopausal symptoms in menopausal women with an intact uterus receiving combination MHT compared with MPA. This claim was adequately supported.
- 6.80 The submission described MP as superior in terms of reducing the risk of progestogen-associated breast cancer in menopausal women with an intact uterus receiving combination MHT compared with MPA and norethisterone. While MP may be associated with a lower risk of breast cancer compared to MPA, the following uncertainties should be noted:
- The observational nature of the included studies and the post hoc within-study indirect treatment comparison (ITC) conducted in the submission comparing MP and MPA, using no MHT as a comparator.
 - The main evidence (which also informed the economic evaluation) was based on a retrospective population-based cohort study conducted in South Korea (Yuk, 2024). It lacked details on treatment patterns (continuous or cyclical) and did not adjust for factors such as BMI, smoking, alcohol, or physical exercise.
 - Based on the results of the post hoc within-study ITC, a notable discrepancy was observed in the reported breast cancer risk reduction, with a hazard ratio (HR) of 0.33 (95% CI: 0.15, 0.71) in Yuk (2024) compared to an odds ratio (OR) of 0.77 (95% CI: 0.43, 1.40) in Abenheim et al., 2022.
 - Abenheim et al., 2022 may be more applicable to the Australian population than Yuk (2024), as it was conducted in the UK and adjusted for important breast cancer risk factors such as age, BMI, smoking status, alcohol consumption,

hysterectomy, oophorectomy, history of endometrial cancer, family history of breast cancer, and oral contraceptive use.

- 6.81 The PSCR acknowledged that the claim of reduced breast cancer risk was based on observational study data, however claimed this was the best evidence available as no RCTs were identified.
- 6.82 The ESC considered that the claim that MP has superior safety compared to MPA in terms of reducing the risk of breast cancer was supported by evidence, but the magnitude of the effect was uncertain due to lack of robust evidence and the uncertainties outlined in paragraph 6.80. The ESC noted that there are differences in breast cancer epidemiology between different populations, and that the population in the Abenhaim study was likely more applicable to the Australian population, however also noted it was an observational study. The pre-PBAC response acknowledged the uncertainties in the magnitude of reduction of breast cancer risk with MP compared to MPA, however claimed this largely related to applicability issues associated with both studies cited, including location, timeframe and confounding. It claimed that the magnitude of difference in breast cancer risk between MP and MPA may lie somewhere between the two estimates calculated from the results of the Yuk and Abenhaim studies.
- 6.83 The submission described MP as non-inferior in terms of AEs of treating menopausal symptoms in menopausal women with an intact uterus receiving combination MHT compared with MPA. This claim was adequately supported.
- 6.84 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.85 The PBAC considered that the claim of superior comparative safety with regards to breast cancer risk was not adequately supported by the data.

Estrogel Pro

Consumer comments

- 6.86 The PBAC noted and welcomed the input from individuals (187), health care professionals (18) and organisations (4 – Sexual Health and Family Planning ACT (SHFPACT) Canberra Menopause Centre (CMC); RANZCOG; Women’s Health & Research Institute of Australia; Inherited Cancers Australia) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with estradiol and progesterone, including preventative health benefits such as that on bone health and metabolic disease; improving menopausal symptoms including hot flushes, aches and pains, and sleep and mood disturbances; being body identical and effective; a better safety profile compared to MHT products PBS-listed (improved safety and lower breast cancer risk with Prometrium versus older progestogens; transdermal estrogens do not increase VTE risk and are not contraindicated in patients with VTE or migraines with aura); improved relationships and energy levels; improved quality of life and ability to contribute in the workforce;

- being easier to use and titrate doses compared to other therapies (although one comment stated patches were easier to use than the gel); and availability of supply compared to other MHT products that are in shortage. One comment noted Estrogel Pro is one of the only MHT options for patients with migraine, and one individual commented on the importance of having a range of MHT products available on the PBS, as individuals may respond differently to different products.
- 6.87 Some individuals stated they had experienced no AEs from this treatment, while others commented on side effects they experienced, including bloating and headaches when increasing or decreasing the estrogen dose, and sore breasts.
- 6.88 Comments stated that menopausal symptoms affect quality of life, including causing sleep disturbance, brain fog and mood changes, impacting individuals' social life, and inability to continue working without treatment to improve symptoms.
- 6.89 The cost of a private prescription for Estrogel Pro was identified as the major barrier to access, particularly if required long term, and the cost on the private market creates equity of access issues. One comment stated the Estrogel Pro pack was economical if two pumps daily of Estrogel was being used, otherwise patients will run out of Estrogel or Prometrium first, and expressed a desire to have the individual products available.
- 6.90 Inherited Cancers Australia (which provided comments for all three submissions) noted many women in their community experience menopause at an earlier age and for longer, due to factors such as risk reducing surgery for ovarian cancer or treatment for cancer, and having more MHT options available on the PBS will allow increased access for more women and help to reduce these challenges.
- 6.91 The SHFPACT CMC stated that most prescribers will prescribe transdermal estrogen as observational data shows non-oral estrogen has a lower risk of thromboembolic events compared to oral therapy. Until recently this has been prescribed as patches or the transdermal gel currently listed on the PBS, however there have been supply issues with MHT products for the past several years, the patches require adherence to a twice weekly regimen which can be an adherence issue for some patients, the adhesive in the patch may lead to contact dermatitis, and the patch can leave an adhesive ring at the patch site that is unsightly and difficult to remove. Estrogel has a number of advantages compared to other estradiol transdermal products, including improved adherence compared to patches due to daily dosing, and easier titration of dosing compared to the estradiol gel currently PBS-listed. SHFPACT/CMC stated current evidence suggests MP is the optimal progestogen choice, it is less likely to attenuate the beneficial effects of estrogen on lipoprotein metabolism, and may have a lower risk of breast cancer.
- 6.92 The Women's Health & Research Institute of Australia commented that there are a number of disadvantages with MHT products currently PBS-listed. Estradiol patches have been intermittently available due to shortages, and many women do not tolerate the adhesive patches. In addition, many women cannot take oral estradiol due to the risk of thrombosis. Progestins currently available have AEs including oedema, tender

breasts, worsening of pre-menstrual symptoms and pre-menstrual dysphoric disorder, can trigger suicidal thoughts or severe mental health issues, and synthetic progestins have a higher breast cancer risk than Prometrium. It commented that the combination pack is a safe, first-line choice for menopause treatment for most women with a uterus, and has a range of health benefits such as preventative bone and cardiovascular benefits.

- 6.93 The PBAC noted input from RANZCOG welcoming the consideration of multiple medications for women's health. Whilst they did not comment on specific medications they expressed concern for the market cost of medication for some patients, such as MHT. It supported the PBS listing wherever possible of appropriate medications.

Clinical claim

- 6.94 In women with an intact uterus with symptoms of estrogen deficiency seeking MHT, the submission described EstroGel Pro medicine pack as equivalent or non-inferior in terms of effectiveness and safety compared to the individual components of EstroGel and MP administered in combination.

Economic analysis

Estradiol

- 6.95 The submission presented a cost-minimisation and a revealed preference approach for EstroGel versus Sandrena based on the claim of non-inferior efficacy and safety.
- 6.96 The submission proposed an approved ex-manufacturer price (AEMP) of \$ [REDACTED] per pack of EstroGel based on two key steps:
- Cost minimised price of EstroGel versus Sandrena per day of treatment; and
 - A revealed preference study (a proxy willingness to pay [WTP] study), where the differences in patient costs between private EstroGel versus R/PBS Sandrena reflect the value that women place on the attributes of EstroGel.
- 6.97 The equi-effective doses were estimated as: 1.5 mg of EstroGel (2.5 g of gel contains 1.5 mg estradiol) is equi-effective to 1.0 mg of Sandrena (1 sachet or 1 g contains 1 mg estradiol). The equi-effective doses of EstroGel and Sandrena were based on the recommended dosing regimens in their respective Product Information. The dosing regimens were consistent with the dosing protocols applied in the EstroGel (Archer et al., 2003 and Archer et al., 2012) and Sandrena (Hedrick et al., 2009 and Hedrick et al., 2010) trials. Notably, the clinical trials also included lower doses of both EstroGel (1.25 g of gel containing 0.75 mg estradiol) and Sandrena (0.25 mg and 0.5 mg estradiol).
- 6.98 The results of the CMA based on cost per day for Sandrena are presented in Table 14.

Table 14: Results of the cost-minimisation approach

	Component	Sandrena	Estrogel	Calculation
A	AEMP	\$11.32	-	
B	Pack size (g)	28	80	
C	Dose per unit (g)	1	1.25	
D	Doses per pack	28	64	b / c
E	Dose/day (g)	1	2.5	
F	Doses per day	1 per day	2	e / c
G	Duration of pack (days)	28	32	d / f
H	Cost per day	\$0.40	\$0.40 ^a	a / g
I	AEMP	\$11.32	\$12.94	g x h

Source: Table 3.2, p156 of the submission main body.

AEMP = approved ex-manufacture price; g = grams

^a Estrogel price per day set to Sandrena price per day

- 6.99 The cost-minimised AEMP of \$12.94 for an 80 g pump pack of Estrogel (32 days of treatment) was calculated using the cost per day of \$0.40 for Sandrena (\$11.32/28 days). The CMA approach presented by the submission was appropriate.
- 6.100 The submission proposed an AEMP of \$█ for Estrogel, which is \$█ higher than the price calculated using the CMA. The submission sought to justify this price increase through a revealed preference (proxy WTP) study. The methodology for the revealed preference study and its reliability to serve as a proxy for a WTP study was not presented in the submission.
- 6.101 The submission claimed that the 75,000 Australian women and their clinicians who used Estrogel or Estrogel Pro in June 2024 were fully aware of the choice between Sandrena and Estrogel, but preferred Estrogel and were willing to pay an additional cost for the attributes of Estrogel, such as formulation, presentation, ease of titration and safety profile. The submission claimed that there is a preference for Estrogel and considered this Revealed Preference Analysis a proxy for a WTP study, justifying a higher price of Estrogel over Sandrena. A patient satisfaction survey (N=156) conducted by the sponsor revealed that only seven patients (4%) switched from Sandrena to Estrogel. The reasons for switching included unavailability (n=3), perceived low effectiveness (n=2), clinician recommendation (n=1), and safety concerns (n=1). Factors such as clinicians' recommendation or shortage of transdermal patches may not reflect women's preferences to Estrogel.
- 6.102 As presented Table 15, the submission compared market prices of Estrogel from five online pharmacies (range: \$30.99 to \$44.88) and R/PBS price for Sandrena 1 mg/g gel sachets (range: \$0.00 to the dispensed price for maximum quantity [DPMQ] of \$25.63 with an average copayment of \$18.64). The current DPMQ for Sandrena 1 mg/g gel x 28 sachets is \$25.63, and \$37.81 for the MDQ of 2 x 28 sachets.

Table 15: Calculation of the price difference of Estrogel vs Sandrena based on revealed preferences – cost to patient

Calculation	Private Estrogel	R/PBS Sandrena 1 mg/g 28 sachets [#]	Difference
Low (lowest Estrogel private vs. highest Sandrena PBS)	\$30.99	\$25.63 ^{a#}	\$5.36
High (highest Estrogel private vs. lowest Sandrena PBS)	\$44.88	\$0.00	\$44.88
Average (average 5 online pharmacies for Estrogel vs. weighted average copayment for Sandrena)	\$35.17	\$18.58 ^a	\$16.59

Source: Table 3.3, p157 of the submission main body.

NA = not applicable; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^aThe submission used 2023/2024 value as the comparison was based on 2023 utilisation.

[#]corrected during evaluation.

6.103 The submission stated that the additional costs that women chose to pay for Estrogel in 2023 ranged from \$0 to \$44.88, and thus a higher price of \$1 (\$1 higher than the cost-minimised price) could be justified. This approach to seek a higher price may not be appropriate as the submission did not present the proportion of women who opted for low, high, average, or no extra payment. Furthermore, the WTP may be influenced by factors such as income, product availability, or clinicians' recommendations. This WTP approach may not represent the value-based price from a health system perspective.

Progesterone

6.104 The submission presented a CEA of MP compared to MPA based on the claim of superior safety in reducing the risk of progestogen-associated breast cancer.

6.105 The key components of the economic evaluation are presented in Table 16.

Table 16: Summary of key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis.
Perspective	Healthcare system.
Treatments	MP versus MPA.
Outcomes	Cost per breast cancer case avoided. Cost to avoid one life year lost.
Therapeutic claim: effectiveness	MP is non-inferior in terms of efficacy for protecting against the development of estrogen-associated endometrial hyperplasia compared to MPA. MP is non-inferior in terms of efficacy for preserving the effectiveness of estrogen at treating menopausal symptoms compared to MPA.
Therapeutic claim: safety	MP is superior in terms of safety for reducing the risk of progestogen-associated breast cancer compared to MPA and norethisterone. MP is non-inferior in terms of side effects of treating menopausal symptoms compared to MPA.
Time horizon	One year.
Software package	Excel.

Source: Adapted from Table 3.4, p158 of the submission main body.

MP= micronised progesterone; MPA= medroxyprogesterone acetate

6.106 The submission conducted CEA to translate the superior safety of MP (reduced breast cancer cases) into cost savings, and to compare these cost savings to the incremental cost of treatment with MP.

- 6.107 The submission calculated the number needed to treat (NNT) to avoid one breast cancer patient using breast cancer rates by type of progesterone based on Yuk (2024). As discussed in paragraph 6.63 and shown in Table 12, Yuk (2024) reported 123 cases per 100,000 person-years with MP treatment compared with 320 cases per 100,000 person-years with MPA. Consequently, the submission calculated 197 fewer cases of breast cancer with MP, resulting in an NNT of 507 person-years.
- 6.108 The estimated cost of one year of treatment per person with MP is \$ [REDACTED] (\$ [REDACTED] per pack x 10.71 packs per year) and MPA is \$ [REDACTED] (\$ [REDACTED] per pack x 6.52 packs per year), resulting in an incremental cost per person year of \$ [REDACTED]. Based on an NNT of 507, the incremental cost of MP to avoid one case of breast cancer is therefore \$155,000 to < \$255,000 (\$ [REDACTED] x 507). This was based on the DPMQ prices for both MP and MPA.
- 6.109 The submission estimated the cost of breast cancer care to be \$80,932 for five years. This was derived from Goldsbury et al. (2018)⁷, an Australian study, which reported annual mean health system costs by cancer type from 2006-2010. The costs, including Medicare and PBS claims, inpatient hospital episodes and emergency department presentations, were adjusted to 2024 dollars using Australian Bureau of Statistics (ABS) health inflation index. The submission excluded any cost beyond five years, such as end of life costs. This was appropriate.
- 6.110 Data for the loss of life expectancy (LOLE) due to breast cancer was based on an Australian study by Baade et al., 2015.⁸ The study estimated the LOLE to be between 4.1 and 6.9 years at the median age of breast cancer diagnosis (57 years), with mortality follow-up to 2010. Being a relatively old study, the data may not accurately reflect recent improvements in breast cancer survival. However, the submission conservatively used the lower LOLE estimate of 4.1 years and did not include loss of quality of life in the analysis.
- 6.111 The results of the CEA are presented in Table 17.

⁷ Goldsbury, D. E., Yap, S., Weber, M. F., Veerman, L., Rankin, N., & et al, (2018), 'Health services costs for cancer care in Australia: Estimates from the 45 and Up Study', PLoS ONE, 13(7): e0201552.

⁸ Baade, P. D., Youlden, D. R., Andersson, T. M., Youl, P. H., Kimlin, M. G., et al, (2015), 'Estimating the change in life expectancy after a diagnosis of cancer among the Australian population', BMJ Open, 5:e006740.

Table 17: Results of the stepped economic evaluation

Step and component	MP	MPA	Increment
Step 1: NNT with MP to avoid one case of breast cancer per year of treatment versus MPA			
Breast Cancer rate (with EV as estrogen)	0.00122737	0.003199269	
Cases per 100,000 person years	123	320	-197
NNT with MP to avoid 1 case of breast cancer			507
Step 2: incremental cost of MP per breast cancer case avoided			
DPMQ	\$█	\$█	
Pack size	30	56	
Capsules/day	0.88	1	
Pack duration (days)	34.12	56.00	
Packs per year	10.71	6.52	
Cost per patient per year	\$█	\$█	\$█
Incremental cost of MP to avoid one case of breast cancer			\$█ ¹
Step 3: cost offset due to avoiding cost of breast cancer care over the first five years from diagnosis			
Cost of managing one breast cancer patient after first five years from diagnosis			\$80,932
Net cost to the Australian health system of one breast cancer case avoided due to use of MP			\$█
Step 4: incorporation of LOLE from breast cancer			
Loss of life expectancy per one breast cancer diagnosis (years)			4.1
Cost to avoid one life year lost			\$█ ²

Source: Table 3.7, p161 of the submission main body.

DPMQ = dispensed price for maximum quantity; EV = estradiol valerate; LOLE = loss of life expectancy; MP= micronised progesterone; MPA= medroxyprogesterone acetate; NNT = number needed to treat

The redacted values correspond to the following ranges:

1 \$155,000 to < \$255,000

2 \$25,000 to < \$35,000

6.112 The incremental cost to avoid one breast cancer case was calculated at \$155,000 to < \$255,000, with \$█ as the net cost to the Australian health system. Additionally, the incremental cost to avoid one life year lost was calculated at \$25,000 to < \$35,000. The incremental cost to avoid one breast cancer case was uncertain due to the uncertainty in the ITC results based on Yuk (2024), as described in paragraph 6.80.

6.113 Breast cancer rate of MP compared to MPA was a key input that affected the results of the analysis. Based on clinical evidence presented in the submission, although MP may be associated with lower risk of breast cancer than MPA, the relative magnitude was uncertain. As outlined in paragraph 6.68, reduction in breast cancer rates with MP might have been overestimated in Yuk (2024) compared to Abenheim et al. (2022). Therefore, an additional scenario analysis, presented in Table 18, was conducted by applying the OR reported by Abenheim et al. (2022) to the MPA breast cancer risk from Yuk (2024) to estimate the breast cancer risk for MP, acknowledging differences in what OR and HR represent.

Table 18: Scenario analyses conducted during evaluation

Step and component	MP	MPA	Increment
Step 1: NNT with MP to avoid one case of breast cancer per year of treatment versus MPA			
Breast Cancer rate	0.00247 ^a	0.003199269 ^b	
Cases per 100,000 person years	247	320	-73
NNT with MP to avoid 1 case of breast cancer			1,371
Step 2: incremental cost of MP per breast cancer case avoided			
DPMQ	\$█	\$█	
Pack size	30	56	
Capsules/day	0.88	1	
Pack duration (days)	34.12	56.00	
Packs per year	10.71	6.52	
Cost per patient year	\$█	\$█	\$█
Incremental cost of MP to avoid one case of breast cancer			\$█ ^{c1}
Step 3: cost offset due to avoiding cost of breast cancer care over the first five years from diagnosis			
Cost of managing one breast cancer patient after first five years from diagnosis			\$80,932
Net cost to the Australian health system of one breast cancer case avoided due to MP use			\$█
Step 4: incorporation of LOLE from breast cancer			
Loss of life expectancy per one breast cancer diagnosis (years)			4.1
Cost to avoid one life year lost			\$█ ²

Source: Adapted from Table 3.7, p161 of the submission main body and Attachment 5- Economic Analysis for all MHT to the submission.

DPMQ = dispensed price for maximum quantity; EV = estradiol valerate; LOLE = loss of life expectancy; MP = micronised progesterone; MPA = medroxyprogesterone acetate; NNT = number needed to treat

^aThe breast cancer rate for MP was estimated by applying the OR reported by Abenhaim et al. (2022) to the MPA breast cancer rate from Yuk (2024).

^b the rate of breast cancer in women receiving MPA reported in Yuk (2024) study

^c Incremental cost per patient year multiplied by NNT

The redacted values correspond to the following ranges:

1 \$455,000 to < \$555,000

2 \$95,000 to < \$115,000

6.114 Applying the OR of 0.77 (95% CI: 0.43, 1.40) from Abenhaim et al. (2022) to estimate the NNT with MP, increased the incremental cost to avoid one breast cancer case from \$155,000 to < \$255,000 to \$455,000 to < \$555,000 and the incremental cost to avoid one life year lost from \$25,000 to < \$35,000 to \$95,000 to < \$115,000. The pre-PBAC response stated that use of results from Abenhaim may be a worst-case scenario, and claimed that MP could be considered cost-effective at any odds ratio between 0.33 and 0.66. The pre-PBAC response claimed that the inclusion of quality-of-life benefits would be expected to further improve the cost-effectiveness of MP.

Estrogel Pro

6.115 The submission presented a CMA based on the sum of components pricing. As stated in paragraph 5.4, the choice of the comparator for Estrogel Pro was the concomitant use of the two individual components, Estrogel and MP. Consequently, the price requested for Estrogel Pro was based on a discount applied to the sum of the component pricing of Estrogel and MP.

6.116 Table 19 summarises the results of the sum of component pricing.

Table 19: Results of sum of component pricing

	Component	AEMP	DPMQ	Calculation
A	Estrogel	\$	\$	
B	MP	\$	\$	
C	Sum of components	\$	\$	A+B
D	Estrogel Pro proposed	\$	\$	
E	Discount vs. Sum of components (\$)	-\$	-\$	D-C
F	Discount vs. Sum of components (%)	-21.9%	-30.8%	E/C

Source: Table 3.8, p162 of the submission main body.

AEMP = approved ex-manufacture price; DPMQ = dispensed price for maximum quantity; MP= micronised progesterone.

6.117 The submission proposed an AEMP of \$ (DPMQ: \$) for Estrogel Pro which was 22% (DPMQ: 31%) lower than the sum of components.

6.118 As stated in paragraph 5.5, in practice, Estrogel Pro could replace other PBS-listed MHTs. However, no evidence was provided that Estrogel Pro provides a significant improvement in efficacy and/or safety over PBS-listed combination MHTs, such as combination MHT patches with estradiol and norethisterone (Estalis Continuous 50/140, Estalis Continuous 50/250, Estalis Sequi 50/140, Estalis Sequi 50/250) or PBS-listed estrogen preparations in combination with a PBS-listed progesterone.

Drug cost/patient/year: \$ (Estrogel), \$ (Prometrium), \$ (Estrogel Pro)

6.119 One pack of 80 g pump pack of Estrogel provides treatment for 32 days. Based on the proposed DPMQ of \$, the estimated cost per patient per year of treatment with Estrogel was \$ (\$ x [365.25/32] days).

6.120 Using a weighted dosing for cyclical (24 capsules per cycle; 68%) and continuous (25 capsules per cycle; 38%) regimen, a pack of MP would last on average for 34 days. Based on the proposed DPMQ of \$, the estimated cost per patient per year of treatment with MP was \$ (\$ x [365.25/34] days).

6.121 The duration of treatment was 32 days based on the individual component of Estrogel in the pack. Based on the proposed DPMQ of \$, the estimated cost per patient per year of treatment with Estrogel Pro was \$ (\$ x [365.25/32] days). Assuming each pack of Estrogel Pro would last 32 days, there will be a small amount of wastage associated with MP (34 days in the pack).

Estimated PBS usage & financial implications

Estradiol

6.122 This submission was not considered by DUSC.

6.123 The submission presented a market share approach to estimate the financial impact of listing Estrogel as an MHT. The submission stated that listing of Estrogel is expected to capture significant market share through two primary populations: (i) the substitution of Sandrena on the R/PBS and (ii) transition of patients from the private

market of Estrogel to R/PBS. The sources of data used in the financial estimates are presented in Table 20 below.

Table 20: Key inputs for financial estimates for Estrogel

Parameter	Value applied and source	Comment
Population 1: Substitution of Sandrena on R/PBS		
Total prescriptions for Sandrena	█ ¹ in Year 1, increasing to █ ² in Year 6; based on the PBS item statistics for Sandrena (8286D) as well as under copayment data for Sandrena for the year 2022-2023, and applying a 6.2% rate of change over the next six years.	Uncertain. The dataset for the under-copayment data does not perfectly align with the calendar year used in the PBS item statistics.
Uptake rate	10% in Year 1 increasing to 27.5% in Year 6; based on Sponsor's assumption.	This was uncertain; no evidence was presented to support this assumption.
Script equivalence of Sandrena vs Estrogel	0.88:1	This was reasonable.
Population 2: Transition from private market to R/PBS		
Estrogel private market	█ ³ in Year 1, increasing to █ ⁴ in Year 6; based on private market data for MP source by the sponsor from 2020-2024. A growth rate of 30% was applied in Year 1, decreasing to 6% by Year 6.	This was likely underestimated. The average year-on-year growth rate from 2021 to 2024 was approximately 88%.
Uptake rate	75% in Year 1, increasing to 100% in Year 2 onwards; based on sponsor's assumption that 100% of patients from the private market will transition to R/PBS.	This was reasonable.
Prescription dispensed per patient per year	11.41 prescriptions; given that treatment duration with Estrogel is expected to last 32 days.	This was reasonable.
Costs		
Estrogel	Requested DPMQ of \$ █.	This was reasonable; however, the submission did not use the DPMQ related to 60-day dispensing.
Sandrena	DPMQ: \$25.63 (PBS item 8286D).	
Patient copayment	PBS: \$22.93 and RPBS: \$6.03; 99.48% PBS and 0.50% RPBS based on PBS item statistics for Sandrena.	This was reasonable.

Source: Table 4.2, p168; Table 4.3, p168; Table 4.4, p169; Table 4.5, p171; Table 4.6, p171; and Table 4.7, p171 of the submission main body and Attachment 6.1-Estrogel Utilisation and Costs Model to the submission.

DPMQ = Dispensed Price for Maximum Quantity; MHT = Menopause hormone therapy; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ 100,000 to < 200,000

² 200,000 to < 300,000

³ 30,000 to < 40,000

⁴ 40,000 to < 50,000

6.124 Table 21 presents the estimated financial implications of listing Estrogel.

Table 21: Estimated use and financial implications for Estrogel

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated Population 1 ^{a#}	1	1	1	1	1	1
Number of scripts dispensed Population 1 ^b	2	3	3	4	5	5
Number of patients treated Population 2 ^{a#}	4	4	5	5	5	5
Number of scripts dispensed Population 2 ^b	6	7	7	8	8	8
Estimated financial implications of Estrogel						
Cost to R/PBS less copayments	9	9	9	9	9	9
Estimated financial implications for Sandrena						
Cost to R/PBS less copayments	10	10	10	10	10	10
Net financial implications						
Net cost to R/PBS	9	9	9	9	9	9

Source: Table 4.8, p172, Table 4.9, p172, Table 4.11, p173; Table 4.12, p174 of the submission main body.

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Back calculating the number of patients treated with Estrogel, assuming 11.41 prescriptions per year as estimated by the submission.

^b Assuming 11.41 prescriptions per year as estimated by the submission.

[#]calculated during evaluation.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 10,000 to < 20,000

³ 20,000 to < 30,000

⁴ 30,000 to < 40,000

⁵ 40,000 to < 50,000

⁶ 200,000 to < 300,000

⁷ 400,000 to < 500,000

⁸ 500,000 to < 600,000

⁹ \$0 to < \$10 million

¹⁰ net cost saving

6.125 The total cost to the R/PBS of listing Estrogel was estimated to be \$0 to < \$10 million in Year 6 (50,000 to < 60,000 patients), and a total of \$40 million to < \$50 million in the first 6 years of listing. There was a net cost to the R/PBS due to transition of patients from the private market to the R/PBS and a higher price proposed for Estrogel (\$1 compared to cost-minimised price of \$27.37). Although the increase in patient numbers was reasonable, the requested DPMQ for Estrogel was not justified, as outlined in paragraph 6.103.

6.126 The utilisation/financial estimates for Estrogel were considered uncertain due to the following issues:

- For Population 1, the estimated number of prescriptions for Sandrena was based on PBS item statistics report (8286D) and under copayment data for 2022-2023. While this approach is reasonable, the under-copayment data does not perfectly align with the calendar year used in the PBS item statistics, and the data may not reflect the increased use of Sandrena due to the ongoing shortage of patches in Australia.

- The uptake rate of 10% in Year 1, increasing to 27.5% by Year 6, was based on the sponsor's assumption and lacked supporting evidence.
- For Population 2, the submission did not provide any evidence to support the assumption of 30% private market growth in Year 1, decreasing to 3% in Year 6. There was, on average, 89% year-on-year increase in the number of packs dispensed for Estrogel in the private market from 2021 to 2023, with this trend continuing into 2024. The submission attributed this growth partly to preference of Estrogel over Sandrena as well as supply issues for patches and projected that growth would flatten. The market for Estrogel could be larger than estimated as the estimates did not account for patients who are currently using other forms of estrogens for MHT (both PBS and non-PBS listed) who may switch to Estrogel if listed on the PBS.

Progesterone

6.127 This submission was not considered by DUSC.

6.128 The submission used a market share approach to estimate the use and financial impact of listing MP as an MHT. The submission stated that the listing of MP is expected to capture a significant market share through two populations: (i) the substitution of MPA (5 mg and 10 mg) and norethisterone 5 mg on the R/PBS, and (ii) the transition of patients from the private market to R/PBS. The sources of data used in the financial estimates are presented in Table 22 below.

Table 22: Key inputs for financial estimates for MP

Parameter	Value applied and source	Comment
Population 1: Substitution of MPA and norethisterone on R/PBS		
Total prescriptions for MPA 5 mg	█ ¹ in Year 1, decreasing to █ ² in Year 6 based on the PBS item statistics report for MPA 5 mg (2323G) and under copayment data for 2022-2023, and applying a simple average of the growth change over the past three years to project a continued annual decline in services of 9.75%.	Uncertain. The dataset for the under-copayment data does not perfectly align with the calendar year used in the PBS item statistics. Furthermore, the decline in services was based on PBS item statistics which may not reflect actual utilisation.
Total prescriptions for MPA 10 mg	█ ³ in Year 1 decreasing to █ ³ in Year 6 based on the PBS item statistics report for MPA 10 mg (2321E) and under copayment data for 2022-2023 and applying a simple average of the growth change over the past three years to project a continued annual decline in services of 3.26%.	Uncertain. The dataset for the under-copayment data does not perfectly align with the calendar year used in the PBS item statistics. Furthermore, the decline in services was based on PBS item statistics which may not reflect actual utilisation.
Total prescriptions for norethisterone 5 mg	█ ⁴ per year based on PBS statistics item report for norethisterone 5 mg (2993M) for the Year 2023 and assuming a zero rate of change over the next six years.	This estimate was reasonable, though uncertain, given that services for norethisterone 5 mg year-to-date through June 2024 reached 52% of the total services recorded in 2023.
Proportion used applicable to the proposed indication of MHT	90% of PBS services for MPA (5 mg and 10 mg) were assumed to be related to MHT, while 35% of PBS services for norethisterone was assumed to be related to MHT.	This was uncertain as there is no clear data regarding the proportion of MPA (5 mg and 10 mg) and norethisterone use specifically associated with MHT.

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Parameter	Value applied and source	Comment
Uptake rate	60% in Year 1, increasing to 92.5% in Year 6 for both MPA (5 mg and 10 mg) and norethisterone; based on sponsor's assumption.	This was uncertain as was an assumption with no supporting evidence.
Script equivalence (MPA [5 mg and 10 mg] versus MP)	1:1.64	This was reasonable and aligns with the recommended dosing in the respective PI of MPA and MP.
Script equivalence (norethisterone 5 mg versus MP)	1:1.76	This was reasonable and aligns with the recommended dosing in the respective PI of norethisterone and MP.
Population 2: Transition from private market to R/PBS		
MP private market	█ in Year 1, increasing to █ by Year 6; based on private market data for MP source by the sponsor from 2020-2024. A growth rate of 12% was applied in Year 1, decreasing to 3% by Year 6.	This was likely underestimated, given there was, on average, a 31% year-on-year increase in the number of packs dispensed for MP in the private market from 2021 to 2023, with this trend continuing into 2024.
Uptake rate (switch from private market to R/PBS)	75% in Year 1, increasing to 100% in Year 2 onwards; based on sponsor's assumption that 100% of patients from the private market will transition to R/PBS.	This was reasonable.
Prescriptions dispensed per patient per year	10.71 scripts; given that treatment duration with MP is expected to last 34.12 days.	This was reasonable.
Costs		
MP	Requested DPMQ of \$ █	This was reasonable; however, the submission did not use the DPMQ related to 60-day dispensing.
MPA 5 mg	DPMQ: \$18.94 (PBS item: 2323G)	
MPA 10 mg	DPMQ: \$20.33 (PBS item: 2321E)	
Norethisterone	DPMQ: \$35.67 (PBS item: 2993M)	
Co-payment	PBS: \$19.92 and RPBS: \$6.22 based on weighted average copayments for norethisterone 5 mg.	This was reasonable.
Co-payment	PBS: \$19.92 and RPBS: \$6.22; 99.87% PBS and 0.13% RPBS.	This was reasonable.

Source: Table 4.16, p181; Table 4.17, p181; Table 4.18, p182; Table 4.19, p184; Table 4.20, p184; Table 4.21, p184; and Section 4.2 of the submission main body, and Attachment 6.2-Prometrium Utilisation and Costs Model to the submission.

DPMQ = dispensed price for maximum quantity; MHT = menopause hormone therapy; MP = micronised progesterone; MPA = medroxyprogesterone acetate; PBS = Pharmaceutical Benefits Scheme; PI = product information; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

- 1 30,000 to < 40,000
- 2 10,000 to < 20,000
- 3 20,000 to < 30,000
- 4 100,000 to < 200,000
- 5 40,000 to < 50,000
- 6 50,000 to < 60,000

6.129 Table 23 presents the estimated financial implications of listing MP.

Table 23: Estimated use and financial implications for MP

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated Population 1 ^{a#}	1	2	2	2	2	2
Number of scripts dispensed Population 1 ^b	3	3	3	3	3	3
Number of patients treated Population 2 ^{a#}	4	5	5	6	6	6
Number of scripts dispensed Population 2 ^b	7	8	9	9	9	9
Estimated financial implications of MP						
Cost to R/PBS less copayments	10	10	10	10	10	10
Estimated financial implications for MPA (5 mg and 10 mg) and norethisterone						
Cost to R/PBS less copayments	11	11	11	11	11	11
Net financial implications						
Net cost to R/PBS	10	10	10	10	10	10

Source: Table 4.22, p185 and Table 4.26, p187 of the submission main body.

MP = micronised progesterone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Back calculating the number of patients treated with MP assuming 10.71 prescriptions per year as estimated by the submission.

^b Assuming 10.71 prescriptions per year as estimated by the submission.

[#]calculated during evaluation.

The redacted values correspond to the following ranges:

- 1 5,000 to < 10,000
- 2 10,000 to < 20,000
- 3 100,000 to < 200,000
- 4 30,000 to < 40,000
- 5 40,000 to < 50,000
- 6 50,000 to < 60,000
- 7 300,000 to < 400,000
- 8 400,000 to < 500,000
- 9 500,000 to < 600,000
- 10 \$10 million to < \$20 million
- 11 net cost saving

6.130 The total cost to the R/PBS of listing MP was estimated to be \$10 million to < \$20 million in Year 6 (60,000 to < 70,000 patients), and a total of \$90 million to < \$100 million in the first 6 years of listing.

6.131 The utilisation/financial estimates for MP were considered uncertain due to the following issues:

- For Population 1, the estimated number of prescriptions for MPA 5 mg and 10 mg were based on PBS item statistics report (2323G and 2321E) and under copayment data for 2022-2023. While this approach is reasonable, the under-copayment data does not perfectly align with the calendar year used in the PBS item statistics.
- The proportion of prescriptions applicable to the proposed MHT indication was uncertain due to the multiple TGA indications, six for norethisterone and four for MPA (5 mg and 10 mg).
- For Population 2, the submission did not provide any evidence to support the assumption of 12% private market growth in Year 1, decreasing to 3% in Year 6.

There was, on average, a 31% year-on-year increase in the number of packs dispensed for MP in the private market from 2021 to 2023, with this trend continuing into 2024. As a result, the growth rate of the private market of MP was underestimated.

Estrogel Pro

6.132 This submission will not be considered by DUSC.

6.133 The submission used a market share approach to estimate the use and financial impact of listing Estrogel Pro as an MHT. The submission anticipated that, upon listing, 100% of eligible women would transition to R/PBS listings within one year, driven by the cost savings for patients. The sources of data used in the financial estimates are presented in Table 24 below.

Table 24: Key inputs for financial estimates for Estrogel Pro

Parameter	Value applied and source	Comment
Estrogel Pro private market	█ ¹ women in Year 1, increasing to █ ² women in Year 6; based on the private market data for Estrogel Pro sourced by the sponsor from 2020-2024. A growth rate of 30% was applied to the 2024 data in Year 1, gradually decreasing to 2% in Year 6.	No evidence was provided to support the assumed market growth rate.
Uptake rate	75% in Year 1, increasing to 100% in Year 2 onwards; based on sponsor's assumption that 100% of patients from the private market will transition to the R/PBS due to cost-savings.	This was reasonable.
Scripts dispensed per patient per year	11.41 scripts; given that treatment duration with Estrogel Pro is expected to last 32 days based on the individual component of Estrogel.	This was reasonable; however, there will be wastage with the individual component of MP which, on average, is expected to last 34 days.
Cost of Estrogel Pro	Requested DPMQ of \$█; based on the cost-minimised price using the sum of component pricing approach outlined in the economic evaluation.	This was consistent with Section 3.
Patient copayment	PBS: \$22.93 and RPBS: \$6.03, based on a distribution of 99.48% PBS and 0.50% RPBS, as per Sandrena PBS item statistics 8286D.	This was reasonable.

Source: Table 4.304, p194; Table 4.31, p194; Table 4.324, p195; Section 4.3.2.3, p195; Section 4.3.2.4, p195 of the submission main body and Attachment 6.3-Estrogel Pro Utilisation and Costs Model to the submission.

DPMQ = Dispensed price for maximum quantity; MHT = menopause hormone therapy; MP = micronised progesterone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

1 40,000 to < 50,000

2 60,000 to < 70,000

6.134 Table 25 presents the estimated financial implications of listing Estrogel Pro.

Table 25: Estimated use and financial implications for Estrogel Pro

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	2	2	3	3	3
Number of scripts dispensed ^a	4	5	5	6	6	6
Estimated financial implications of Estrogel Pro						
Cost to R/PBS less copayments	7	8	8	8	8	8

Source: Table 4.324, p195 and Table 4.334, p195 of the submission main body.

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Assuming 11.41 scripts per year as estimated by the submission.

The redacted values correspond to the following ranges:

1 30,000 to < 40,000

2 50,000 to < 60,000

3 60,000 to < 70,000

4 400,000 to < 500,000

5 600,000 to < 700,000

6 700,000 to < 800,000

7 \$10 million to < \$20 million

8 \$20 million to < \$30 million

6.135 The total cost to the R/PBS of listing Estrogel Pro was estimated to be \$20 million to < \$30 million in Year 6 (60,000 to < 70,000 patients), and a total of \$100 million to < \$200 million in the first 6 years of listing.

6.136 The utilisation/financial estimates for Estrogel Pro were considered uncertain due to the following issues:

- The submission did not provide any evidence to support the assumption of 30% private market growth in Year 1, decreasing to 2% in Year 6. This was likely to be underestimated given there was, on average, a 96% year-on-year increase in the number of packs dispensed for Estrogel Pro in the private market from 2021 to 2023, with this trend continuing into 2024. The submission attributed this growth partly to supply issues for other MHT products and projected that growth would flatten as supply normalises. However, it is uncertain what proportion of patients using other estrogen and combination MHT products may continue to switch to using Estrogel Pro.
- The submission assumed that 100% of the private market would transition to accessing Estrogel Pro on the R/PBS, with no anticipated substitution. Patients using other MHT products such as combination MHT patches, oral combination MHTs, or products containing individual MHT products (both PBS and non-PBS listed) may switch to using Estrogel Pro if listed on the PBS, which is not included in the estimates. Furthermore, Estrogel Pro is likely to replace individual components of Estrogel and MP prescribed concomitantly, given that the supply of Estrogel Pro on the PBS would be one patient co-payment if listed (compared to two co-payments if Estrogel and Prometrium are dispensed separately).

6.137 The PSCR maintained that estimated financial implications provided for Estrogel, Prometrium and Estrogel Pro reflected best estimates, and maintained that the estimates included the main sources for prescriptions of these products.

- 6.138 The ESC considered the estimated patient numbers and growth rate was uncertain for all three products, particularly in the context of shortages for some MHT products.

Financial Management – Risk Sharing Arrangements

- 6.139 The submission did not propose any risk-sharing arrangements.
- 6.140 The submission stated that, due to the risk of lowering the average selling price which would threaten the financial viability of these products, the sponsor is unable to consider a risk sharing arrangement, however is willing to work with the Department to limit use of these products outside the requested population.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of estradiol (Estrogel), progesterone (Prometrium) and estradiol and progesterone (Estrogel Pro) as General Schedule unrestricted benefit listings, and corresponding General Schedule restricted benefit listings for 60-day maximum dispensed quantities.
- 7.2 The PBAC noted these products are currently available on the private market, however cost is a barrier to access. The PBAC noted consumer comments stated it was important to have a range of MHT options available on the PBS, particularly in the context of shortages of other MHT products. Consumer comments also stated these products were effective in managing symptoms of menopause and provided benefits compared to other MHT products currently PBS-listed. In the context of limited clinical evidence, the PBAC found the consumer comments particularly useful in articulating patient-relevant outcomes, especially those from people currently supplied these products on the private market.
- 7.3 The PBAC also noted priority area actions in the National Women's Health Strategy, including removing barriers to support equitable access to timely, appropriate and affordable care for all women, and to support women and health care providers to manage the effects of menopause; and recommendations from the report from the Senate inquiry into issues related to menopause and perimenopause. The PBAC considered there was a public health need to have a range of clinically appropriate MHT options listed on the PBS.
- 7.4 The PBAC considered Sandrena as the nominated comparator for Estrogel to be reasonable, and considered other non-oral forms of estrogen for MHT could also be comparators (e.g. patches). The PBAC considered MPA as the nominated comparator for Prometrium to be reasonable. The PBAC considered the individual components of Estrogel and Prometrium as the nominated comparators for Estrogel Pro were not true comparators, and considered other forms of MHT (e.g. combination MHT patches) would be more appropriate comparators.
- 7.5 The PBAC considered there was sufficient evidence that Estrogel, Prometrium and

Estrogel Pro are at least as effective as comparator products for the primary outcomes. In addition, each product may offer small differences compared to MHT options currently PBS-listed, however this was difficult to quantify and the PBAC considered these differences to be marginal and/or highly uncertain.

- 7.6 The PBAC noted that trials presented in the submission were generally older and there was variability in the type and severity of symptoms in the population, which has implications for study design and treatment outcome. The PBAC considered evidence demonstrated non-inferior efficacy of these products compared to the comparators. However, for some outcomes there may be evidence of benefit:
- The PBAC noted that the submission claimed Estrogel had an additional benefit of preventing osteoporosis in postmenopausal women at high risk of future fractures, but noted this benefit was not modelled. The PBAC noted the submission's claim that Estrogel may have a lower incidence of skin irritation and itchiness compared to Sandrena. While no evidence was provided to support the claim of reduced skin irritation with Estrogel, the pre-PBAC response claimed that propylene glycol is associated with allergic contact dermatitis and this is present in Sandrena but not Estrogel. This adverse effect is also in the Product Information for Sandrena, but not for Estrogel. The PBAC noted consumer comments and the sponsor hearing stated there was a risk of skin irritation with Sandrena. The PBAC noted consumer comments stating that the Estrogel pump pack allows greater flexibility of dosing, the gel is easy to use, quick to dry and does not leave a sticky residue.
 - The PBAC considered the claim MP has a lower breast cancer risk compared to MPA was uncertain. While some studies suggest MP may be associated with a lower risk of breast cancer compared to MPA, the studies were observational in nature and post hoc within-study ITC compared MP and MPA, and the main evidence was based on a retrospective population-based cohort study conducted in South Korea. In addition, based on the results of the post hoc within-study ITC, a notable discrepancy was observed in the reported breast cancer risk reduction, and a further analysis did not conclude there was any benefit of a reduced risk of breast cancer. The PBAC also noted NICE guidelines state that there was insufficient evidence to support that one type of progestogen (e.g. MP) may be safer than others. The PBAC concluded that any differences are either marginal or highly uncertain.
- 7.7 The PBAC considered that there was sufficient rationale, in conjunction with a strong public health need and clinical need, to recommend listing these products on the PBS. The PBAC considered there was a need to list both the individual products as well as the combination, to allow options based on individual patient needs.
- 7.8 Given that the PBAC concluded that the extent of added benefit of Estrogel and Prometrium over the comparators is uncertain and likely marginal, the PBAC considered the extent of price premium requested over the comparators was not

adequately justified by the evidence provided. The PBAC also noted the sponsor inputs for current costs of supply for EstroGel, Prometrium and EstroGel Pro. The PBAC noted the proposed AEMP for EstroGel Pro was 22% lower than the sum of the components' proposed AEMPs. The PBAC considered the price proposed for EstroGel Pro would be acceptable. In relation to EstroGel and Prometrium, the PBAC considered that given uncertainties of incremental benefit versus the comparators, a price reduction more consistent with the requested price for EstroGel Pro may be appropriate.

- 7.9 The PBAC advised EstroGel, Prometrium and EstroGel Pro should not be treated as interchangeable with any other drugs.
- 7.10 The PBAC advised that EstroGel, Prometrium and EstroGel Pro are suitable for prescribing by nurse practitioners for continuing therapy only.
- 7.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for EstroGel, Prometrium and EstroGel Pro:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies, as there is insufficient evidence to demonstrate superior efficacy, and evidence demonstrated non-inferior safety, of these medicines compared to comparators;
 - b) The treatment is not expected to address a high and urgent unmet clinical need due to other MHT products being available;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.12 The PBAC noted that these submissions are not eligible for an Independent Review because they received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new items:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL					
estradiol 0.06% (750 microgram/actuation) gel, 64 actuations	NEW MP NP	1	1	5	EstroGel
Restriction Summary: Unrestricted / Treatment of Concept: NEW					
Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)					

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	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction type: <input checked="" type="checkbox"/> Unrestricted benefit
	Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
	Administrative Advice: Estradiol should be used in conjunction with progestogen in women with an intact uterus.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL					
estradiol 0.06% (750 microgram/actuation) gel, 64 actuations	NEW MP NP	2	2	5	Estrogel
Restriction Summary: 14238 / Treatment of Concept: 14238					
	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"/> Restricted benefit				
	Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.				
	Administrative Advice: Estradiol should be used in conjunction with progestogen in women with an intact uterus.				
	Indication: The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient.				

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PROGESTERONE					
progesterone 100 mg capsule, 30	NEW	1	30	5	Prometrium
Restriction Summary: Unrestricted / Treatment of Concept: NEW					
	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				
	Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.				

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PROGESTERONE					
progesterone 100 mg capsule, 30	NEW	2	60	5	Prometrium
Restriction Summary: 14238 / Treatment of Concept: 14238					
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"/> Restricted benefit					
Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
Indication: The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient.					

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL & PROGESTERONE					
progesterone 100 mg capsule [30] (& estradiol 0.06% (750 microgram/actuation) gel [64 actuations], 1 pack	NEW MP NP	1	1	5	Estrogel Pro
Restriction Summary: Unrestricted / Treatment of Concept: NEW					
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					
Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESTRADIOL & PROGESTERONE					
progesterone 100 mg capsule [30] (& estradiol 0.06% (750 microgram/actuation) gel [64 actuations], 1 pack	NEW MP NP	2	2	5	Estrogel Pro
Restriction Summary: 14238 / Treatment of Concept: 14238					
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"/> Restricted benefit					
Administrative Advice: Continuing Therapy Only:					

		For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
		Indication: The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient.

These restrictions may be subject to further review. Should there be any changes made to the restrictions 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

Besins Healthcare acknowledges the deep consideration of this submission by the PBAC and the strong collaboration to make these products available to Australian women through the PBS.