# 5.05 ESTRADIOL WITH PROGESTERONE, Capsule containing estradiol 1 mg (as hemihydrate) with progesterone 100 mg, BIJUVA®, Theramex Australia Pty. Ltd.

## 1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Unrestricted Benefit listing and a corresponding General Schedule Restricted Benefit listing for 60-day maximum dispensed quantities (MDQ) for estradiol 1 mg (as hemihydrate) with progesterone 100 mg capsule (hereinafter referred to as Bijuva®) for the treatment of moderate to severe vasomotor symptoms (VMS) in postmenopausal women.

1.2 Listing was requested on the basis of a cost-minimisation approach versus Estrogel® Pro.

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

| Component | Description |
|---|---|
| Population | Postmenopausal women with an intact uterus experiencing estrogen deficiency symptoms |
| Intervention | Bijuva (estradiol and progesterone) oral capsules, 1 mg/100 mg |
| Comparator | • Estrogel 0.06% (estradiol hemihydrate) gel pump pack<br>• Prometrium 100 mg (progesterone) oral capsules |
| Outcomes | Primary:<br>• Reduction in frequency of moderate to severe VMS at Week 4 and Week 12<br>• Reduction in severity of moderate to severe VMS at Week 4 and Week 12<br>• Endometrial safety (incidence of endometrial hyperplasia at 12 months)<br>Secondary:<br>• Quality of life improvements (MENQOL)<br>• Sleep quality improvements (MOS-Sleep Scale)<br>• Overall safety and tolerability |
| Clinical claim | Bijuva (combination estradiol-progesterone oral capsules) is non-inferior to Estrogel in treating estrogen deficiency symptoms in postmenopausal women, based on indirect comparison methodology |

Source: Table 1-2, p15 of the submission main body.
MENQOL = Menopause-specific Quality of Life Questionnaire, MOS = Medical Outcomes Study; VMS = vasomotor symptoms.

## 2 Background

### *Registration status*

2.1 Bijuva was Therapeutic Goods Administration (TGA) registered on 3 May 2022 for continuous combined hormone replacement therapy for estrogen deficiency symptoms in postmenopausal women with an intact uterus and with at least 12 months since last menses.

### *Senate inquiry into the issues related to menopause and perimenopause*

2.2 The submission claimed that listing Bijuva on the Pharmaceutical Benefits Scheme (PBS) would address the terms of the Senate inquiry[1] into the issues related to menopause and perimenopause, highlighting the following recommendations from the inquiry report as relevant to this submission:

- Recommendation 16: The committee recommends that the Department of Health and Aged Care, including the TGA, 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.

### *National Women's Health Strategy 2020-2030*

2.3 The submission referred to the National Women's Health Strategy 2020-2030[2], and stated that listing Bijuva 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.

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[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

[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

2.4 The Pre-Sub-Committee Response (PSCR) claimed that the proposed listing of Bijuva addresses the unmet need highlighted in the Senate inquiry. The PSCR stated that Bijuva provides an additional bioidentical MHT option to Estrogel Pro, and claimed that listing Bijuva on the PBS will allow for better individualised treatment which cannot be achieved with only one treatment option available. The evaluation noted that although Estrogel Pro is a bioidentical MHT listed on the PBS, there are also other MHT products currently PBS-listed. The ESC agreed there was a potential unmet need with respect to access to MHT products, particularly due to ongoing shortages of other MHT products PBS-listed, which could also impact other MHT products that are PBS-listed.

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

# 3 Requested listing

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price for Max. Qty | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| ESTRADIOL + PROGESTERONE | | | | | |
| estradiol 1 mg + progesterone 100 mg capsule, 28 | $56.02* | 1 | 1 | 5 | Bijuva |
| | | | | | |
| **Category / Program:** General Schedule | | | | | |
| **Prescriber type:** ☒Medical Practitioners ☒Nurse practitioners | | | | | |
| **Restriction type:** ☒Unrestricted benefit | | | | | |
| **Prescribing Instructions:** 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. | | | | | |

*calculated during the evaluation reflecting updated mark-up prices as of July 2025.

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price for Max. Qty | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| ESTRADIOL + PROGESTERONE | | | | | |
| estradiol 1 mg + progesterone 100 mg capsule, 28 | $98.26* | 2 | 2 | 5 | Bijuva |
| | | | | | |
| **Category / Program:** General Schedule | | | | | |
| **Prescriber type:** ☒Medical Practitioners ☒Nurse practitioners | | | | | |
| **Restriction type:** ☒ Restricted benefit | | | | | |
| **Prescribing Instructions:** 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:** The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient. | | | | | |

*calculated during the evaluation reflecting updated mark-up prices as of July 2025.

3.1 The submission requested a listing for Bijuva with a maximum quantity of 28 capsule (1 pack) and 5 repeats, which will provide approximately 6 months' worth of

treatment at a dose of 1 capsule daily, and a corresponding 60-day Restricted Benefit listing of a maximum quantity of 2 packs (2 x 28 capsules) and 5 repeats for approximately 12 months' worth of treatment. The requested restrictions are consistent with the PBS restrictions for Estrogel Pro.

3.2 The submission requested medical practitioners and nurse practitioners for continuing therapy only (CTO) as the authorised prescriber types for the Bijuva listings, consistent with the current PBS listings for Estrogel Pro.

3.3 At its July 2025 meeting, the PBAC recommended the removal of the CTO note for estradiol 0.06% (750 microgram/actuation) gel (Estrogel®), progesterone 100 mg capsule (Prometrium®) and Estrogel Pro, without further restrictions placed on nurse practitioners, to be consistent with its November 2024 consideration of listings with a nurse practitioner CTO note. The PBAC was requested to advise if the CTO note should also be removed for Bijuva, if recommended for listing.

3.4 Continued Dispensing (CD) arrangements do not currently apply to Estrogel Pro or other PBS-listed menopause hormonal therapy (MHT) medicines. The PBAC was requested to advise whether CD arrangements should also not apply for Bijuva.

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

# 4 Population and disease

4.1 Menopause is a natural, age-related biological process that marks the end of a woman's reproductive years. Post-menopause is defined as the permanent cessation of menstrual cycles for at least 12 months due to the loss of ovarian function, accompanied by a sustained decline in circulating estrogen and progesterone. In Australia, the average age at natural menopause is between 50.5 and 51.2 years.[3]

4.2 Menopause is frequently associated with debilitating symptoms, including vasomotor disturbances, mood changes, joint pain, fatigue, and cognitive issues, which can significantly affect quality of life, productivity, and relationships for women with moderate to severe symptoms. Menopause is also associated with an increased risk of osteoporosis and cardiovascular disease. In Australia, up to 80% of women experience menopausal symptoms, and around 30% report symptoms severe enough to significantly interfere with their daily lives.[4] VMS are among the most frequently reported and burdensome complaints, with 74.2% of postmenopausal women under 55 years and 42.1% of those aged 60–65 years experiencing them, with moderate to

[3] Davis et al. (2015), 'Menopause', Nature Reviews Disease Primers, vol 1 (15004), doi:10.1038/nrdp.2015.
[4] Herson & Kulkarni, (2022), 'Hormonal Agents for the Treatment of Depression Associated with the Menopause', Drugs & Aging, vol 39, https://doi.org/10.1007/s40266-022-00962-x.

severe symptoms reported by 28.5%, 15.1%, and 6.5% of women under 55, 55–59, and 60–65 years, respectively.[5]

4.3 Postmenopausal women with an intact uterus who experience symptoms of estrogen deficiency, the target population, currently have access to both hormonal and non-hormonal treatment options. MHT is recognised as the most effective treatment and is considered first-line for symptomatic women.[6] For postmenopausal women with an intact uterus, combined estrogen-progestogen therapy is required to prevent endometrial hyperplasia and reduce the risk of endometrial cancer.

4.4 Bijuva is the first and only TGA approved combination of bioidentical estradiol (1 mg) and bioidentical micronised progesterone (MP) (100 mg) in a single daily oral capsule. Estradiol substitutes for the loss of estrogen production in postmenopausal women and alleviates menopausal symptoms by reducing the number and intensity of hot flushes associated with menopause. MP acts to oppose the development of endometrial hyperplasia caused by estrogens and reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women. The submission stated that the listing of Bijuva would expand the therapeutic options in practice, providing an alternative to current transdermal and oral MHT formulations.

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

# 5 Comparator

5.1 The submission nominated Estrogel Pro, a combination pack containing estradiol transdermal gel (0.06%; 0.75 mg/actuation) and MP capsules (100 mg) as the main comparator. The main argument provided in support of this nomination was that Estrogel Pro is the only combination bioidentical MHT that contains the same active ingredients as Bijuva listed on the PBS. The submission also stated that the use of Estrogel Pro is supported under Recommendation 19 of the inquiry report, as referenced in paragraph 2.2. The ESC noted that while oral progesterone 100 mg capsules (in Prometrium and the progesterone component in Estrogel Pro) is the only micronised progesterone currently PBS-listed, estradiol (as hemihydrate) is currently listed on the PBS in the following forms: 2 mg tablet (Zumenon®); gel sachets (Sandrena®), patches (e.g. Estradot®, Estraderm®) and topical gel (Estrogel).

5.2 The nominated comparator may not be appropriate. Oral estradiol tablets were previously considered to be inappropriate comparators for transdermal estradiol gels (paragraph 5.2, estradiol and progesterone, Public Summary Document [PSD], November 2024 PBAC Meeting). This view was based on the evidence that oral estrogen carries a higher risk of venous thromboembolism (VTE) than transdermal

[5] Gartoulla, et al. (2015), 'Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years', The Journal of the North American Menopause Society, vol 22 (7), 10.1097/GME.0000000000000383.

[6] The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2023, 'Managing Menopausal Symptoms', Clinical Guidance.

estrogen, and that oral estrogen is contraindicated in patients with risk factors for VTE or cardiovascular disease, elevated triglycerides, liver disease, or gallbladder disease.

5.3 The PSCR argued that both Bijuva and Estrogel Pro have the same contraindications in their Product Information (PI), with no difference in contraindications with cardiovascular conditions, liver disease or gallbladder disease, and no difference in the conditions requiring supervision or reasons for immediate withdrawal of therapy included in the PIs.

5.4 The PSCR claimed that there is limited evidence to demonstrate differences in cardiovascular risk with Bijuva compared to transdermal MHT. The PSCR also stated that in menopausal women with elevated VTE, stroke or cardiometabolic risk, transdermal estrogens have lower risk than comparable oral therapy.

5.5 More relevant comparators may include PBS-listed Femoston® (oral estradiol + dydrogesterone) or oral estradiol tablets with MP capsules.

5.6 The submission argued that Femoston may not be an appropriate comparator because it does not align with the preferred combination of estradiol and MP, and that it follows a cyclical regimen rather than a continuous regimen. The submission also noted that Femoston contains a synthetic progestin and therefore does not meet the comparator selection criteria outlined in Recommendation 19 of the inquiry report, as referenced in paragraph 2.2. The PSCR and pre-PBAC response (PSCR) reiterated that the nominated comparator was aligned with Recommendation 19 of the Senate inquiry report, and claimed data demonstrates non-inferiority between Bijuva and Estrogel Pro. The PSCR also argued that Femoston is not an appropriate comparator because it is not bioidentical, and that it is used by a patient population independent to patients suitable for Bijuva. The ESC agreed that Femoston was a cyclical regimen, compared to Bijuva which provided the same dose of MHT continuously. Estrogel Pro can also be administered in a cyclical regimen (topical estradiol daily with oral progesterone 100 mg daily for days 1-25 of each cycle, or oral progesterone 200 mg daily for 12 days in the last half of the cycle (days 15-26), and both dydrogesterone and MP provide effective endometrial protection when combined with estradiol.

5.7 Additionally, the submission stated that no 1 mg estradiol hemihydrate, the estradiol form in Bijuva and Estrogel Pro, oral tablets are listed on the PBS. While PBS-listed Progynova®, an estradiol valerate oral tablet, can be used with PBS-listed Prometrium®, a bioidentical MP oral capsule, the estradiol valerate has a different chemical structure compared to estradiol hemihydrate and requires cleavage either during absorption by the intestinal mucosa or first pass metabolism in the liver, to be converted into estradiol and valeric acid.

5.8 Combination patches were not considered appropriate comparators because of the different mode of delivery. While this was reasonable, it was inconsistent with the selection of Estrogel Pro as a comparator, where the estradiol component also differs in its mode of delivery compared to Bijuva.

5.9 The ESC noted the submission nominated Estrogel Pro as the comparator on the basis that it is the only bioidentical MHT product PBS-listed, and Recommendation 19 from the Senate inquiry report. The ESC noted the submission stated it did not include MHT

patches as comparators due to the different mode of delivery to Bijuva, however also noted that Estrogel Pro has a different mode of delivery for its estrogen component.

5.10 The ESC noted evidence demonstrates different risks with the use of MHT depending on individual patient factors. In women in menopause with an increased risk of VTE, stroke or cardiometabolic risk, the use of transdermal estrogen is lower risk than a comparable dose of oral estrogen. Limited evidence has shown that, in postmenopausal women with average risk <60 years of age, there has not been shown to be an increased risk of VTE, stroke or cardiovascular events with the use of low-dose oral estrogens (1 mg 17β-estradiol or 0.45 mg conjugated estrogens), although additional data from adequately powered studies will increase knowledge in this area.[7]

5.11 The ESC considered other forms of MHT could be considered alternative comparators, and patients using an MHT patch may switch to Bijuva if they were unable to tolerate topical therapy.

5.12 The ESC therefore advised that Estrogel Pro is an appropriate comparator. However, as Estrogel Pro contains a topical gel, it is reasonable to also include other topical MHT products listed on the PBS containing an estrogen + progestogen as alternative comparators (e.g. MHT patches such as estradiol + norethisterone acetate patches [Estalis® Continuous]). The ESC advised that Femoston may not be an appropriate comparator as it is not listed on the PBS for a continuous therapy regimen (14 days estradiol and 14 days estradiol + dydrogesterone), whereas Estrogel Pro provides either estradiol daily with progesterone for 12 days in the last half of the cycle, or estradiol daily with progesterone for days 1-25 of each cycle (paragraph 5.6).

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

# 6 Consideration of the evidence

## *Sponsor hearing*

6.1 There was no hearing for this item.

## *Consumer inputs*

6.2 The PBAC noted and welcomed the input from individuals (33), health care professionals (26) and organisations (6) via the Office of Health Technology Assessment Consultation Hub. Health care professionals commented that menopausal symptoms are unique for each individual, and some individuals experience severe symptoms that impact their ability to function. Symptoms can affect productivity, relationships and careers, and cause issues such as anxiety, depression and difficulty coping. The input stated that MHT is the most effective treatment for controlling symptoms, and MHT is effective for most individuals at a low

[7] Black, D., 2020, 'The safety of oral versus transdermal estrogen', available at https://menopause.org.au/images/stories/education/docs/nams/nams-practice-pearl-oral-vs-transdermal-estrogen.pdf

dose, but some may require higher doses. Health care professionals commented that estradiol with progesterone is the only oral MHT option that contains body-identical estradiol and MP, and has the potential to provide more consistent dose-response results than transdermal therapy or combination oral therapy. Both health professionals and consumers raised that the cost of estradiol with progesterone was a barrier to access.

6.3 One comment from a health care professional stated that there is no long-term head-to-head data available comparing estradiol with progesterone to transdermal MHT, however input stated that interim data (2-4 years) is promising. Input commented on the favourable tolerance and safety profile of body-identical hormones compared to synthetic MHT. Input also commented on the increased risk of VTE associated with estradiol and progesterone, and that it is unsuitable for individuals at a high risk of cardiovascular disease. Comments identified side effects with MP included sedation, gastrointestinal symptoms and dizziness, but these can be partly managed with night-time administration.

6.4 Health care professionals commented that the single-dose, oral form may improve adherence and therefore reduce risk of endometrial hyperplasia, carcinoma and unscheduled bleeding, and may reduce the risk of individuals adjusting the estrogen dose without medical supervision. One comment stated that improved ease of administration is important for individuals with limited health literacy.

6.5 Health care professionals commented that listing estradiol with progesterone on the PBS would support equitable access to a range of MHT options, particularly for individuals who require MHT but where transdermal or synthetic hormones are not appropriate or not preferred. With supply issues preventing access to multiple other MHT products, there is a current lack of combined MHT on the PBS.

6.6 Individuals commented on the challenges of menopause symptoms, resulting in declines to physical and mental health, affecting relationships and the ability to work. The benefits of MHT included reduced anxiety; improved bone, heart and brain health; improved sleep quality; and reduction in hot flushes and night sweats. One comment stated there was an improved ability to function after treatment with estradiol with progesterone.

6.7 Individuals also commented on a lack of effective MHT options for individuals who cannot absorb medication transdermally, tolerate synthetic hormones or have allergies, and that an estradiol with progesterone capsule is convenient and reduced the risk of inconsistent hormone delivery through cream and patches. Comments also stated that there was a need for subsidised access to a range of MHT options, and the current cost of estradiol with progesterone was causing financial barriers.

6.8 Sexual Health Victoria and WellFemme Telehealth Menopause Clinic commented that estradiol with progesterone as an oral preparation is an option for individuals who have impaired absorption of transdermal estrogen, and the combined preparation can assist with adherence, leading to better symptom management and reduce the risk of accidental unopposed estrogen exposure if progesterone is not taken at the same

time as the estrogen. Sexual Health Victoria stated that, as an oral preparation, it would not be suitable for some individuals, such as those with a high risk of VTE or cardiovascular events. It commented that the listing of MP on the PBS has decreased the financial barrier to this medication, however currently individuals who want to use MP but do not or cannot use a transdermal estrogen are unable to access this medication in a combined preparation, limiting access and choice.

6.9 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists commented that costs of new medicines can be prohibitive for patients, and inclusion of these new medicines on the PBS can address some concerns around cost and access. Advanced Pharmacy Australia and the Australasian Menopause Society commented that listing estradiol with progesterone provides an additional treatment option for people living with menopause.

6.10 The Australian College of Nurse Practitioners (ACNP) commented on a range of benefits for estradiol with progesterone, including providing effective symptom relief, tolerability, improved adherence being a single capsule, providing an alternative MHT option for individuals who cannot use patches or topical gel, and equity of access if PBS listed. The ACNP also commented that it would be beneficial to include nurse practitioners as eligible prescribers for Bijuva to support equitable access.

## *Clinical trials*

6.11 No head-to-head trials comparing Bijuva to Estrogel Pro were available. Therefore, the submission was based on two indirect treatment comparisons (ITCs):

- An anchored unadjusted ITC of a Bijuva trial (REPLENISH) versus an Estrogel study (Archer et al., 2003) via a common placebo comparator arm comparing the efficacy (change from baseline in frequency and severity of VMS), and safety (adverse events [AEs]) at Week 12. Although this analysis was based on Estrogel rather than the nominated comparator, Estrogel Pro, this was considered reasonable as VMS are primarily driven by declining estrogen levels in menopause. The PBAC had previously considered the results of Archer et al. (2003) in the November 2024 consideration of Estrogel Pro.
- An unanchored unadjusted ITC of a Bijuva trial (REPLENISH) versus an Estrogel Pro study (Pélissier et al. 2001) comparing the incidence of endometrial hyperplasia.

6.12 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials/studies and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Bijuva trial** | | |
| REPLENISH NCT01942668 | A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study to Evaluate the Safety and Efficacy of Estradiol in Combination with Progesterone in Postmenopausal Women with an Intact Uterus: Estradiol to Reduce the Frequency and Severity of Vasomotor Symptoms and Progesterone to Manage the Incidence of Endometrial Hyperplasia (TXC12-05). | Clinical Study Report, 22 Sept 2017. |
| | Archer, DF, Bernick BA and Mirkin S. A combined, bioidentical, oral, 17β-estradiol and progesterone capsule for the treatment of moderate to severe vasomotor symptoms due to menopause. | Expert Rev Clin Pharmacol 2019; 12(8):729-39. |
| | Constantine, GD, Revicki, AD, Kagan, R, et al. Evaluation of clinical meaningfulness of estrogen plus progesterone oral capsule (TX-001HR) on moderate to severe vasomotor symptoms. | Menopause 2019; 26(5): 513-9. |
| | Kagan, R, Constantine, G, Kaunitz, AM, et al. Improvement in sleep outcomes with a 17β-estradiol-progesterone oral capsule (TX-001HR) for postmenopausal women. | Menopause 2018; 26(6):622-8. |
| | Kaunitz, AM, Bitner, D, Constantine, GD, et al. 17β-estradiol/progesterone in a single, oral, softgel capsule (TX-001HR) significantly increased the number of vasomotor symptom-free days in the REPLENISH trial. | Menopause 2020; 27(12):1382-7. |
| | Lobo, RA, Archer, DF, Kagan, R, et al. A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. | Obstet Gynecol 2018; 132(1):161-70. |
| | Lobo, RA, Liu, J, Stanczyk, FZ, et al. Estradiol and progesterone bioavailability for moderate to severe vasomotor symptom treatment and endometrial protection with the continuous-combined regimen of TX-001HR (oral estradiol and progesterone capsules). | Menopause 2019; 26(7):720-7. |
| | Lobo, RA, Kaunitz, AM, Santoro, N, et al. Metabolic and cardiovascular effects of TX-001HR in menopausal women with vasomotor symptoms. | Climacteric 2019;22(6):610-6. |
| **Estrogel study** | | |
| Archer et al. (2003) | Archer, DF, EstroGel Study Group. Percutaneous 17beta-estradiol gel for the treatment of vasomotor symptoms in postmenopausal women. | Menopause 2003; 10(6):516-21. |
| | Archer, DF, Pickar, JH, MacAllister DC, et al. Transdermal estradiol gel for the treatment of symptomatic postmenopausal women. | Menopause 2012; 19(6):622-9. |
| **Estrogel + micronised progesterone study** | | |
| Pélissier et al. (2001) | Pélissier, C, Maroni M, Yaneva, H, et al. Chlormadinone acetate versus micronized progesterone in the sequential combined hormone replacement therapy of the menopause. | Maturitas 2001; 40(1): 85-94. |

Source: Table 2-5, pp56-60 of the submission main body.

6.13 The key features of the included studies are summarised in Table 3.

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

| Trial | N | Design/ duration | Risk of bias* | Patient population | Outcome(s) |
|---|---|---|---|---|---|
| **Bijuva versus placebo** | | | | | |
| REPLENISH | ES population 1,255; 1/100 = 280 0.5/100 = 303 0.5/50 = 306 0.25/50 = 274 Pbo = 92<br><br>MITT-VMS population 726; 1/100 = 141 0.5/100 = 149 0.5/50 = 147 0.25/50 = 154 Pbo = 135 | Phase III, R, DB, PC, MC, 12 months | Low | Healthy postmenopausal[a] woman of age 40-65 with an intact uterus; screening serum estradiol level of ≤ 50 pg/mL; and BMI ≤ 34 kg/m$^2$. In addition, the MITT-VMS population included women with ≥ 7 moderate to severe hot flushes per day or ≥ 50 per week. | Primary: change in frequency and severity of moderate to severe VMS from baseline to Week 4 and Week 12 (MITT-VMS population).<br>Secondary: mean change in frequency and severity of mild, moderate to severe VMS from baseline; percentage of patients with 50% and separately, 75% reduction in frequency of moderate to severe VMS from baseline at each week up to Week 12; percentage of patients with 50% and separately, 75% reduction in frequency of mild, moderate and severe VMS from baseline at each week up to Week 12; patients with CGI response categories; change from baseline in MENQOL; change from baseline in MOS-sleep (MITT-VMS population).<br>Safety outcomes: AEs (safety population) and incidence of endometrial hyperplasia at 12 months (ES population), |
| **Estrogel versus placebo** | | | | | |
| Archer et al. (2003) | 221; E2 0.75 mg = 75 E2 1.5 mg = 73 Pbo = 73 | Phase III, R, DB, PC, MC 12 weeks | Low to moderate | Healthy postmenopausal[b] women with ≥ 7 moderate to severe hot flushes per day or ≥ 60 per week; body weight not exceeding 130% of ideal weight. | Primary: mean change in frequency of moderate to severe hot flushes from baseline to Week 12.<br>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.<br>Safety outcomes: incidence of treatment emergent signs and symptoms. |
| **Estrogel + MP versus Estrogel + CA** | | | | | |
| Pélissier et al. (2001) | 336; E2+MP = 169 E2+CA = 167 | R, DB, MC, 6 months, followed by 12-month open period | Moderate to high | Healthy postmenopausal[c] women, aged ≤ 57 years with an intact uterus. | Primary: endometrium status<br>Secondary: vaginal bleeding pattern; and climacteric symptoms.<br>Safety outcomes: AEs; metabolic and hepatic parameters. |

Source: Section 2.3.1, pp63-65; Figure 2-3, p70; Figure 2-4, p71; Figure 2-5, p73; Table 2-10, pp75-77 of the submission main body.
*Added during evaluation
1/100 = 1 mg E2/100 mg MP; 0.5/100 = 1 mg E2/100 mg MP; 0.5/50 = 0.5 mg E2/50 mg MP; 0.25/50 = 0.25 mg E2/50 mg MP; AEs = adverse events; BMI = body mass index; CA = chlormadinone acetate; CGI = Clinical Global Impression; DB = double blind; E2 = 17β-estradiol; ES = endometrial safety; FSH = follicle-stimulating hormone; MC = multi-centre; MENQOL = Menopause-specific quality of life; MITT = modified intent to treat; MOS = Medical Outcome Study; MP = micronised progesterone; N = total participants in group; Pbo = placebo; PC = placebo-controlled; R = randomised; VMS = vasomotor symptoms.
[a] Postmenopausal was defined herein as: i) ≥ 12 months of spontaneous amenorrhea, or ii) at least 6 months of spontaneous amenorrhea with a FSH level of > 40 mIU/mL, or iii) ≥ 6 weeks' postsurgical bilateral oophorectomy.
[b] amenorrhoeic either naturally (for at least 6 months) or surgically (with bilateral oophorectomy), and had a serum estradiol concentration no greater than 20 pg/mL, a serum FSH level of at least 40 mIU/mL.
[c] menopause was confirmed with plasma estradiol < 40 pg/mL and FSH > 20 IU/l, or bilateral ovariectomy.

6.14 In REPLENISH, the safety population included all randomised women who took at least one dose of medication; this population was used for the overall safety analysis. The endometrial safety (ES) population included all women randomised to active treatment who completed 12 treatment months and had evaluable baseline and 12-month biopsies; this population was used for the primary safety endpoint analysis of endometrial safety. The modified intent-to-treat vasomotor symptoms (MITT-VMS) population included all treated participants from the VMS sub-study who had measurements of frequency and severity of hot flush data at baseline and at least 1 week during treatment; this population was used for the primary efficacy endpoint analysis. Although the efficacy analysis was 12 weeks, women in the VMS sub-study continued taking medication for 12 months for their potential inclusion in the ES population.

6.15 The eligibility criteria of the included trials were generally aligned with the proposed PBS population. However, there were differences among the trials that may impact the transitivity assumptions of the ITC:

- REPLENISH and Pélissier et al. (2001) included postmenopausal women with intact uterus, whereas Archer et al. (2003) appeared to include both women with and without intact uterus, as endometrial biopsy was performed in some participants. This may reduce comparability for ITC between REPLENISH and Archer et al. (2003) for the assessment of VMS. The PSCR stated that while VMS may occur more frequently in patients who have had a hysterectomy[8], baseline weekly frequency of VMS was similar between the studies. The PSCR claimed that, because of this, there is no expected impact on the ITC VMS outcomes.
- Serum estradiol level at screening varied across the three trials (≤ 50 pg/mL in REPLENISH, ≤ 20 pg/mL in Archer et al., 2003, and < 40 pg/mL in Pélissier et al. 2001). This may favour Archer et al. (2003). The PSCR claimed that while the eligibility cutoffs differed between studies, the actual patient baseline levels were much lower and similar between the studies, and therefore this patient factor is not expected to impact transitivity assumptions around estradiol-related outcomes (e.g. VMS symptom frequency).
- The proportion of white women was lower in REPLENISH (67%), compared to Archer et al. (2003), ranging from 78% to 81% across groups. The proportion of white women was not reported in Pélissier et al. (2001). The impact of this difference was uncertain, although subgroup analyses from REPLENISH indicated more favourable outcomes among white women compared to African American women.
- Patients in REPLENISH and Archer et al. (2003) had comparable body mass index (26.5-26.6 kg/m$^2$ and 26.5-26.7 kg/m$^2$, respectively), which were higher

[8] Wilson, L.F., Pandeya, N., Byles, J., et al., 2016, 'Hot flushes and night sweats symptom profiles over a 17-year period in mid-aged women: The role of hysterectomy with ovarian conservation'. Maturitas 91, pp.1-7.

than those reported in Pélissier et al. (2001) (23.3 kg/m$^2$). This may favour Pélissier et al. (2001), as obesity is a risk factor for endometrial hyperplasia.

- In summary, Archer et al. (2003) included hysterectomised women with lower serum estradiol levels, which may impact the efficacy results. Additionally, the inclusion of a hysterectomised population may underestimate AEs (e.g. uterine haemorrhage in hysterectomised women). REPLENISH applied stricter uterus criteria and had lower proportion of white women, which may affect generalisability to the Australian population.

6.16 The PSCR claimed that the trial populations between the two studies were broadly similar, and none of the differences between the trials invalidated the claim that Bijuva and Estrogel Pro had non-inferior efficacy and safety. The PSCR claimed that the differences were either inconsequential to safety and efficacy findings, or favoured Estrogel Pro (e.g. serum estrogen concentration eligibility cutoff, lower body mass index).

6.17 The primary efficacy outcomes in REPLENISH were change from baseline in frequency and severity of moderate to severe VMS at Week 4 and Week 12. The primary efficacy outcome in Archer et al. (2003) was change from baseline in daily frequency of moderate to severe VMS to Week 12. Daily mean change value was converted to weekly to allow comparison with REPLENISH. The safety outcomes reported across trials included AEs and incidence of endometrial hyperplasia. These outcomes were consistent with the primary endpoints outlined in the draft Food and Drug Administration (FDA) Guidance (2003)[9] and the European Medicines Agency (EMA) Guideline (2005)[10] required for the clinical evaluation of medicinal products for MHT targeting estrogen deficiency symptoms.

## *Comparative effectiveness*

Vasomotor symptoms

6.18 Table 4 presents the change from baseline to Week 12 in weekly frequency of moderate to severe VMS for both Bijuva (MITT-VMS population) and Estrogel (MITT population), along with the results of the placebo-anchored unadjusted ITC.

[9] Food and Drug Administration, (2003), 'Draft Guidance for Industry. Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation,' Available at: www.fda.gov/media/71359/download

[10] European Medicines Agency, (2005), 'Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women,' Available at: www.tga.gov.au/sites/default/files/2024-04/guideline-clinical-investigation-medicinal-products-hormone-replacement-therapy-oestrogen-deficiency-symptoms-postmenopausal-women.pdf

**Table 4: Results of change from baseline to Week 12 in the weekly frequency of moderate to severe VMS in REPLENISH and Archer et al. (2003)**

| Intervention | Bijuva N=141 | Placebo N=135 | LS mean change from baseline vs placebo (95% CI) | SE |
|---|---|---|---|---|
| **REPLENISH (MITT-VMS)[a]** | | | | |
| n | 124 | 115 | **-16.6 (-23.3, -9.8)[a]** | 3.4 |
| Mean baseline (SD) | 72.2 (25.0) | 72.2 (22.7) | | |
| Mean change from baseline (SD) | -55.1 (31.4) | -40.2 (29.8) | | |
| **Archer et al. 2003. (MITT population)[b]** | | | | |
| **Comparator** | **Estrogel 1.25 g N=75** | **Placebo N=73** | **-14.7 (-24.9, -4.5)** | 5.2 |
| n | NR | NR | | |
| Mean baseline (SD)[c] | 72.1 (21.7) | 77.0 (39.2) | | |
| Mean change from baseline (SD)[d] | -54.6 (SE: 3.7)* | -39.9 (SE: 3.6)* | | |
| | **Estrogel 2.5 g N=73** | **Placebo N=73** | **-19.6 (-29.8, -9.4)** | 5.2 |
| n | NR | NR | | |
| Mean baseline (SD)[c] | 73.5 (27.3) | 77.0 (39.2) | | |
| Mean change from baseline (SD)[d] | -59.5 (SE: 3.7)* | -39.9 (SE: 3.6)* | | |
| ITC between Bijuva versus Estrogel 1.25 g/day | | | -1.9 (-14.1, 10.3) | - |
| ITC between Bijuva versus Estrogel 2.5 g/day | | | -3.0 (-9.2, 15.2) | - |

Source: Table 2-21, p106; Table 2-39, p135 of the submission main body.
CI = confidence interval; ITC = indirect treatment comparison; LS = least square; MITT = modified intent to treat; n = number of participants with event; N = total participants in group; NR = not reported; SD = standard deviation; SE = standard error; VMS = vasomotor symptoms.
[a] Mixed model repeated measure analysis (MMRM).
[b] Analysed population is described as a modified ITT population (i.e. patients who took investigational product and had postbaseline outcome assessments). Specific N values are not reported at Week 4 and Week 12.
[c] Baseline values are reported as part of the patient characteristics in Archer et al. (2003) which includes patients in the full randomised population, rather than specifically relating to the analysed populations at Week 4 and 12.
[d] Weekly frequency data was estimated from the daily frequency of moderate to severe VMS as reported in Archer (2003)
**Bold** indicates statistically significant results.
*added based on Attachment 5 to the submission

6.19 In REPLENISH, Bijuva demonstrated a statistically significant reduction in the mean weekly frequency of moderate to severe VMS from baseline to Week 12, compared to placebo, with least square (LS) mean change of -16.6 (95% confidence interval [CI]: - 23.3, -9.8).

6.20 The submission claimed that the level of improvement seen in the primary outcome with Bijuva was clinically meaningful, with a 75% change from baseline (from 72.2 moderate to severe VMS at baseline, reducing to 17.1 at week 12). The submission cited Butt et al. (2007) that a mean 50% improvement was identified as being clinically meaningful. This estimate was uncertain as that study reported a wide CI (32-66%), which was regarded clinically meaningful, and was based on a small sample size (N=17) from a single centre, limiting the generalisability of its findings.

6.21 In addition, the submission proposed a minimal clinically important difference (MCID) of -25 for the change from baseline in the frequency of weekly moderate to severe VMS. This was based on a clinical meaningfulness analysis of the REPLENISH trial, based on the Clinical Global Impression (CGI) improvement. Using the CGI improvement of “minimally improved” versus “much or very much improved”, a

decrease of 36 (at Week 4) to 39 (at Week 12) in the frequency of moderate to severe VMS was considered meaningful. The submission argued that the MCID of -25 can be utilised as a reasonable non-inferiority margin. This was uncertain as the non-inferiority margin of -25 between Bijuva and placebo was determined post-hoc rather than pre-specified.

6.22 In Archer et al. (2003), Estrogel 1.25 g and 2.5 g showed a statistically significant reduction in the mean weekly frequency of moderate to severe VMS from baseline to Week 12, compared to placebo.

6.23 The ITC results showed no significant differences in the weekly frequency of moderate to severe VMS, comparing Bijuva to Estrogel 1.25 g and 2.5 g.

6.24 The ESC noted that the findings in the REPLENISH trial demonstrated that Bijuva improved VMS compared to placebo. The ESC also noted that Bijuva reduced VMS symptoms to a similar extent to both Estrogel 1.25 g and 2.5 g, demonstrating that Bijuva had non-inferior efficacy to the lower dose (1 pump [1.25 g]) of Estrogel as well as the higher dose (2.5 g).

6.25 The submission claimed that the frequency of hot flushes symptoms varied among patients, resulting in a wide 95% CI for treatment differences; however, the magnitude of the mean difference was small, which supported the claim of non-inferiority. This was reasonable; however, no pre-specified non-inferiority margin was available to evaluate the claim.

6.26 The efficacy differences between Bijuva (REPLENISH) and Estrogel (Archer et al. 2003) must be interpreted cautiously given population differences (women with intact uterus in REPLENISH but women with and without uterus in Archer et al. 2003, and different inclusion criteria for baseline estradiol level) (for further details refer paragraph 6.156.14).

6.27 Table 5 presents the change from baseline to Week 12 in severity of mild, moderate and severe VMS for Bijuva (MITT-VMS population) and Estrogel (MITT population), along with the results of the placebo-anchored unadjusted ITC.

**Table 5: Results of change from baseline to Week 12 in the severity of VMS (mild, moderate and severe)* in REPLENISH and Archer et al. (2003)**

| Intervention | Bijuva N=141 | Placebo N=135 | LS mean change from baseline vs placebo (95% CI) | SE |
|---|---|---|---|---|
| **REPLENISH (MITT-VMS)[a]** | | | | |
| n | 124 | 115 | **-0.6 (-0.8, -0.4) [a^]** | 0.1 |
| Mean baseline (SD) | 2.4 (0.3) | 2.3 (0.3) | | |
| Mean change from baseline (SD) | -0.9 (1.0) | -0.4 (0.6) | | |
| **Archer et al. 2003 (MITT population)[b]** | | | | |
| **Comparator** | **Estrogel 1.25 g N=75** | **Placebo N=73** | **-0.5 (NR)** | 0.1 |
| n | 72 | 73 | | |
| Mean baseline (SD) | NR | NR | | |
| Mean change from baseline (SD)[c] | -1.0 (NR) | -0.5 (NR) | | |
| | **Estrogel 2.5 g N=73** | **Placebo N=73** | **-0.8 (NR)** | 0.2 |
| n | 71 | 73 | | |
| Mean baseline (SD) | NR | NR | | |
| Mean change from baseline (SD)[c] | -1.3 (NR) | -0.5 (NR) | | |
| ITC between Bijuva versus Estrogel 1.25 g/day | | | -0.08 (-0.4, 0.3) | - |
| ITC between Bijuva versus Estrogel 2.5 g/day | | | 0.2 (-0.3, 0.7) | - |

Source: Table 2-23, p109; Table 2-39, p135 of the submission main body.
CI = confidence interval; ITC = indirect treatment comparison; LS = least square; MITT = modified intent to treat; n = number of participants with event; N = total participants in group; NR = not reported; SD = standard deviation; SE = standard error; VMS = vasomotor symptoms.
* REPLENISH primary outcome included moderate and severe VMS severity, with any severity (mild, moderate and severe) reported as a secondary outcome. Archer et al. (2003) reported severity for any VMS only, with no published details for moderate and severe VMS severity.
[a] Mixed model repeated measure analysis (MMRM).
[b] Analysed population is described as a modified ITT population (i.e. patients who took investigational product and had postbaseline outcome assessments). Specific N values are not reported at Week 4 and Week 12.
[c] Data estimated in the submission based on Figure 2 in Archer et al. (2003)
**Bold** indicates statistically significant results.
^added based on Attachment 3 Clinical Study Report.

6.28 In REPLENISH, Bijuva demonstrated a statistically significant reduction in the mean severity score of moderate to severe VMS (primary outcome in REPLENISH) from baseline to Week 12, compared to placebo. Likewise, a statistically significant reduction in the mean severity score of mild, moderate and severe VMS (secondary outcome in REPLENISH) from baseline to Week 12 was reported, comparing Bijuva to placebo. The improvements appear modest and may not be clinically meaningful.

6.29 In Archer et al. (2003), Estrogel 1.25 g and 2.5 g showed a significant reduction in the mean severity score of mild, moderate and severe VMS from baseline to Week 12, compared to placebo. The baseline data was missing from the study. Furthermore, severity of moderate to severe hot flushes was not reported in Archer et al. (2003).

6.30 ITC results showed no significant differences in the severity score of mild, moderate and severe VMS, comparing Bijuva to Estrogel 1.25 g and 2.5 g. There were no known non-inferiority margins to evaluate treatment non-inferiority, and the efficacy differences between Bijuva and Estrogel must be interpreted cautiously given population differences (for further details refer paragraph 6.14).

6.31 Table 6 presents the change from baseline to Week 12 in frequency of mild, moderate and severe VMS for Bijuva (MITT-VMS) and Estrogel (MITT), along with the results of the placebo-anchored unadjusted ITC.

**Table 6: Results of change from baseline to Week 12 in the frequency of mild, moderate to severe VMS in REPLENISH and Archer et al. (2003)**

| Intervention | Bijuva N=141 | Placebo N=135 | LS mean change from baseline vs placebo (95% CI) | SE |
|---|---|---|---|---|
| **REPLENISH (MITT-VMS)[a]** | | | | |
| n | 124 | 115 | **-20.6 (-28.3, -12.9)*** | 3.9 |
| Mean baseline (SD) | 86.2 (40.6) | 83.0 (26.5) | | |
| Mean change from baseline (SD) | -60.3 (36.4) | -41.7 (36.4) | | |
| **Archer et al. 2003 (MITT population)[b]** | | | | |
| **Comparator** | **Estrogel 1.25 g N=75** | **Placebo N=73** | **-14.3** (NR) | 7.3 |
| n | 72 | 73 | | |
| Mean baseline (SD) | NR | NR | | |
| Mean change from baseline (SD)[c] | -58.5 (NR) | -44.2 (NR) | | |
| | **Estrogel 2.5 g N=73** | **Placebo N=73** | **-22.0** (NR) | 6.7 |
| n | 71 | 73 | | |
| Mean baseline (SD) | NR | NR | | |
| Mean change from baseline (SD)[c] | -66.2 (NR) | -44.2 (NR) | | |
| ITC between Bijuva versus Estrogel 1.25 g/day | | | -6.3 (-22.6, 9.9) | - |
| ITC between Bijuva versus Estrogel 2.5 g/day | | | 1.4 (-13.8, 16.5) | - |

Source: Table 2-24, p111; Table 2-39, p135 of the submission main body.
CI = confidence interval; ITC = indirect treatment comparison; LS = least square; MITT = modified intent to treat; n = number of participants with event; N = total participants in group; NR = not reported; SD = standard deviation; SE = standard error; VMS = vasomotor symptoms.
[a] Mixed model repeated measure analysis (MMRM).
[b] Analysed population is described as a modified ITT population (i.e. patients who took investigational product and had postbaseline outcome assessments). Specific N values are not reported at Week 4 and Week 12.
[c] Mean change data was estimated in the submission based on Figure 1 of Archer (2003).
**Bold** indicates statistically significant results.
*added based on Attachment 3 Clinical Study Report to the submission

6.32 In REPLENISH, Bijuva demonstrated a statistically significant reduction in the mean weekly frequency of VMS of any severity (mild, moderate and severe) from baseline to Week 12, compared to placebo. It is uncertain if the improvement is clinically meaningful because MCID for the change from baseline in the frequency of weekly mild, moderate and severe VMS, was not available to establish clinical meaningful difference.

6.33 In Archer et al. (2003), Estrogel 1.25 g and 2.5 g showed a statistically significant reduction in the mean weekly frequency of VMS of any severity from baseline to Week 12, compared to placebo. It is uncertain if the improvement is clinically meaningful.

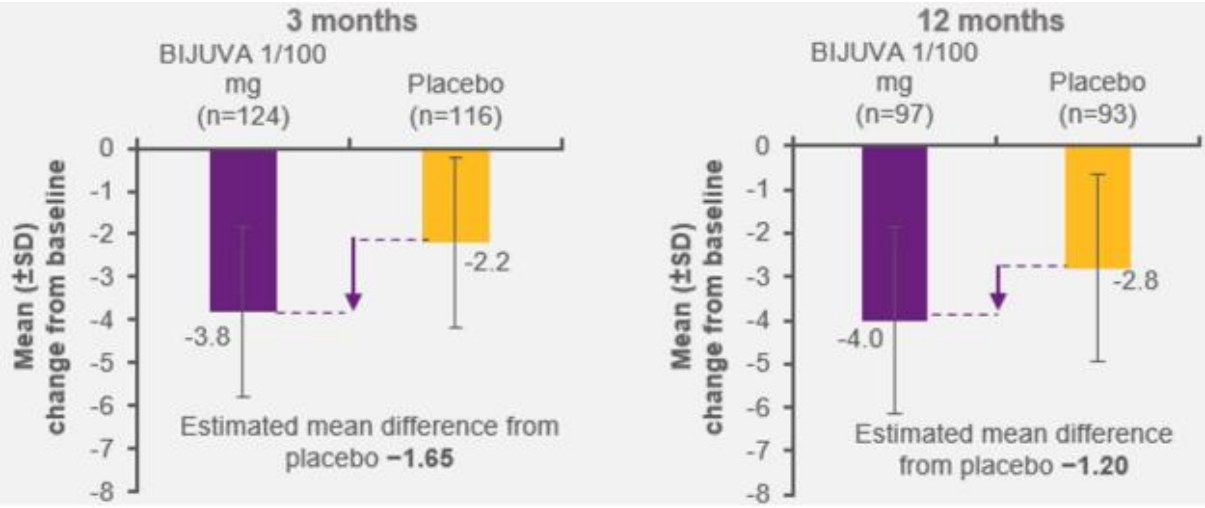
6.34 ITC results showed no significant differences in the weekly frequency of mild, moderate and severe VMS, comparing Bijuva to Estrogel 1.25 g and 2.5 g. There were no known non-inferiority margins to evaluate treatment non-inferiority, and the efficacy differences between Bijuva and Estrogel must be interpreted cautiously given population differences (for further details refer paragraph 6.14).

Quality-of-life outcome

6.35 The quality-of-life outcome using Menopause-specific quality of life (MENQOL) was reported in the REPLENISH trial.

6.36 Figure 1 presents the MENQOL vasomotor domain score in the REPLENISH trial.

**Figure 1: MENQOL vasomotor domain score at Months 3 and 12**




Source: Figure 2-10, p115 of the submission main body.
1/100 = 1 mg estradiol with 100 mg progesterone; MENQOL = Menopause-specific quality of life; n = number of participants with event; SD = standard deviation.
Based on Simon JA et al. (2019) and results from https://clinicaltrials.gov/study/NCT01942668?tab=results

6.37 Bijuva demonstrated a *statistically* significant improvement in MENQOL vasomotor domain and MENQOL total scores at Months 3, 6 and 12, compared to placebo.

6.38 The submission claimed that the differences seen in the MENQOL vasomotor domain were statistically and clinically meaningful, given the MCID was an improvement of ≥1. This was based on Hilditch JR et al. (1996)[11] and Zöllner YF et al. (2005)[12]. This was reasonable and consistent with the recently published Schultz NM et al. (2024)[13] paper which identified ≥0.9 as the clinically important threshold for MENQOL overall score. However, there were limitations in these studies: Hilditch JR et al. (1996) highlighted the uncertainty in the construct validity and test-retest reliability of the vasomotor domain, and Schultz NM et al. (2024) reported moderate test-retest reliability.

6.39 The submission also presented the results of additional secondary efficacy outcomes in the REPLENISH trial:

- Percentage of subjects with 50% and, separately, 75% reduction in frequency of moderate to severe VMS: A statistically significantly higher ≥50% response rate with Bijuva versus placebo (98% versus 67%, risk difference [RD]=21%;

[11] Hilditch JR, Lewis J, et al. (1996), 'A menopause-specific quality of life questionnaire: development and psychometric properties', Maturitas 24(3):161-75. doi: 10.1016/s0378-5122(96)82006-8.
[12] Zöllner YF, Acquadro C, et al. (2005) 'Literature review of instruments to assess health-related quality of life during and after menopause', Qual Life Res 14(2):309-27. doi: 10.1007/s11136-004-0688-z. PMID: 15892422.
[13] Schultz NM, Morga A, et al. (2024), 'Psychometric Evaluation of the MENQOL Instrument in Women Experiencing Vasomotor Symptoms Associated with Menopause', Adv Ther, 41(6):2233-2252. doi: 10.1007/s12325-024-02787-z.

95% CI: 9,33) at Week 12 was reported. Likewise, the results for ≥75% response rate with Bijuva versus placebo (84% versus 37%, RD=36%; 95% CI: 24,47) at Week 12 was reported.

- CGI distribution: 82.1% of the patients in the Bijuva arm reported "very much improved/much improved", compared to 53.4% of the patients in the placebo group, with a RD of 29% (95% CI: 17%, 40%) at Week 12.
- Clinically meaningful analysis: Based on the nonparametric discriminant analysis, the threshold for reporting a meaningful decrease in weekly moderate to severe VMS, based on the best discrimination between women who reported 'minimally improved' and those who reported 'much or very much improved', was a decrease of 36 VMS at Week 4 and a decrease of 39 VMS at Week 12. Based on the CGI analyses, the responder definition should be based on criteria of a decrease of 36 to 39 moderate to severe VMS. As per above definition, 73.4% of the patients in the Bijuva arm were responders, compared to 52.2% of the patients in the placebo group at Week 12.
- Medical Outcome Study (MOS)-Sleep questionnaire: The MOS Total Sleep Score reported statistically significant improvement with Bijuva compared to placebo at Week 12 and Month 6; however, such improvement was not statistically significant at Month 12, with reported LS mean change from placebo of -4.6 (95% CI: -9.4, 0.2). For the domain of Sleep Disturbance, MOS-Sleep scale reported statistically significant improvement with Bijuva compared to placebo at Week 12, Month 6 and 12. No significant differences were reported for the following domains: Sleep adequacy, sleep somnolence, and optimal sleep, at all three time points.

## *Comparative harms*

Endometrial hyperplasia

6.40 Table 7 presents the incidence of endometrial hyperplasia in REPLENISH and Pélissier et al. (2001), along with the results of the unanchored unadjusted ITC. The results were derived from the ES population in REPLENISH, defined as participants with an acceptable baseline biopsy (i.e., at least one biopsy with evaluable tissue showing no evidence of endometrial hyperplasia, cancer, or polyps) and a follow-up biopsy at month 12. In Pélissier et al. (2001), all patients with evaluable samples for biopsies were analysed.

**Table 7: Incidence of endometrial hyperplasia in REPLENISH and Pélissier et al. (2001)**

| Trial ID | Bijuva n/N (%) | Placebo n/N (%) | RD (95% CI) |
|---|---|---|---|
| **REPLENISH (ES population)** | | | |
| Endometrial hyperplasia at Month 12 (%) | 1/268 (0.4%)[a] | 0/85 (0%) | - |
| Upper two-sided limit 95% CI[b] | 1.8% | 3.5% | - |
| | **1.5 mg E2 + MP[c] n/N (%)** | **1.5 mg E2 + CA[d] n/N (%)** | **-** |
| **Pélissier et al. (2001)** | | | |
| Endometrial hyperplasia (%) at Month 6 | 0/146 (0) | 0/148 (0) | - |
| Endometrial hyperplasia (%) at Month 18 | 0/131 (0) | 0/134 (0) | - |
| ITC between Bijuva (at Month 12) versus 1.5 mg E2 + MP (at Month 6) | | | 0.4% (-2.2%, 2.1%) |
| ITC between Bijuva (at Month 12) versus 1.5 mg E2 + MP (at Month 18) | | | 0.4% (-2.5%, 2.1%) |

Source: Table 2-31, p120; Table 2-41, p138; Table 2-42, p121 of the submission main body.
CA = chlormadinone acetate; CI = confidence interval; E2 =17β-estradiol; ES = endometrial safety; ITC = indirect treatment comparison; MP = micronised progesterone; n = number of participants with event; N = total participants in group; RD = risk difference.
[a] One case of simple endometrial hyperplasia without atypia, based on the TGA Product Information
[b] Lower limit not reported
[c] percutaneous 1.5 mg E2 on days 1-24 and oral 200 mg micronised progesterone daily on days 11-24.
[d] percutaneous 1.5 mg E2 on days 1-24 and oral 10 mg chlormadinone acetate daily on days 11-24.

6.41 At Month 12 of the REPLENISH trial, there was one case of endometrial hyperplasia without atypia, and no endometrial cancer was detected in the Bijuva arm. The incidence of endometrial hyperplasia with Bijuva was 0.4% (two-sided upper limit 95% CI: 1.8%), which was below the 95% CI upper limit of the FDA threshold of 4% and EMA threshold of <2%.

6.42 In Pélissier et al. (2001), there were no cases of endometrial hyperplasia reported at Months 6 and 18 among women who used Estrogel and progesterone.

6.43 ITC results showed that the RD in the incidence of endometrial hyperplasia of Bijuva versus Estrogel and progesterone was 0.4%. The submission claimed that the 95% CI was narrow, implying good precision of the unanchored ITC. This was inappropriate as the presented 95% CI of -2.5% to 2.1% was relatively wide compared to the ITC estimate of 0.4%. The results were uncertain due to the unanchored unadjusted ITC of Bijuva versus Estrogel Pro with several study differences: study duration (12 months in REPLENISH versus 18 months in Pélissier et al. 2001), timepoints of outcome measures (12 months in REPLENISH, versus 6 months and 18 months in Pélissier et al. 2001), and study design (randomised controlled trial [RCT] in REPLENISH, versus 6-month RCT, followed by open label study for 12 months in Pélissier et al. 2001).

Treatment-emergent adverse events (TEAEs)

6.44 The submission presented estrogen-related TEAEs from REPLENISH and Archer et al. (2003).

6.45 In REPLENISH, the most common TEAEs reported in ≥5% of patients for Bijuva were breast tenderness (10.8%), headache (7.5%), nasopharyngitis (6.0%), upper respiratory tract infection (5.3%), back pain (5.3%) and abdominal pain (5.3%). The most common treatment-related TEAEs reported for Bijuva were breast tenderness (10.4%), headache (3.4%), vaginal haemorrhage (3.4%) and vaginal discharge (3.4 %).

The most common treatment-related TEAEs with placebo were breast tenderness (0.7%), headache (0.7%), and vaginal discharge (0.7%). There were more patients with at least one treatment-related TEAE in the Bijuva arm, compared to placebo (41.0% versus 17.9%).

6.46 In Archer et al. (2003), the most common TEAEs with Estrogel 2.5 g were headache (19.2%), nausea (12.3%), breast pain (11.0%) and endometrial disorder (8.2%). The most common TEAEs with Estrogel 1.25 g were headache (17.3%), infection (16.0%), breast pain (10.7%) and vaginitis (10.7%). There were more patients with at least one treatment-related TEAE in the Estrogel 2.5 g arm, compared to placebo (45.2% versus 30.1%).

6.47 Study discontinuation due to TEAEs was higher with Bijuva, compared to placebo (10.8% versus 6.6%). Based on the Clinical Study Report for Bijuva, the reasons for study discontinuation due to TEAE with Bijuva were gastrointestinal disorders (1.9%), breast tenderness/swelling (1.6%), and vaginal/uterine haemorrhage (1.2%). In contrast, the reasons for study discontinuation due to TEAE with placebo were palpitation/tachycardia (1.3%) and gastrointestinal disorders (1.3%). No death or life-threatening AEs were reported in both arms; however, there were four life-threatening events experienced in the treatment groups of 0.5 mg estradiol/100 mg MP, 0.5 mg estradiol/50 mg MP, and 0.25 mg estradiol/50 mg MP.

6.48 In the 12-month REPLENISH trial, there were two cases of breast cancer reported in the Bijuva arm, with a case leading to study discontinuation. No breast cancer was reported in the placebo arm. The comparative risk of breast cancer with Bijuva versus Estrogel Pro is unknown due to lack of long-term safety data. Based on the TGA Product Information for both Bijuva and Estrogel, the overall evidence indicates that combined estrogen and progesterone therapy increases the risk of breast cancer, with the risk becoming apparent after approximately three years of use and increasing with longer duration. Continuous combined MHT may offer more consistent protection against irregular and unscheduled breakthrough bleeding, but it has been linked in some observational studies[14] to a slightly higher breast cancer risk, compared to cyclical MHT. In a meta-analysis which included prospective observational studies, there were only a small number of women using micronised progesterone, and its effect on breast cancer risk could not be determined.[14]

6.49 Table 8 presents the results of the ITC of Bijuva versus Estrogel, using placebo as the common comparator, on TEAE and treatment-related TEAE reported in REPLENISH and Archer et al. (2003).

[14] British Menopause Society (BMS), (2020), 'BMS, International Menopause Society, European Menopause and Andropause Society, Royal College of Obstetricians and Gynaecologists and Australasian Menopause Society, (May 2020) Joint Statement on menopausal hormone therapy and breast cancer risk in response to EMA Pharmacovigilance Risk Assessment Committee recommendations'. Available at: https://thebms.org.uk/wp-content/uploads/2020/09/HRT_and_breast_cancer_statement_in_response_to_EMA_PRAC_recommendations_10.9.20.pdf

**Table 8: Results of the indirect comparison of Bijuva versus Estrogel on TEAE and treatment-related TEAE**

| Treatment groups | | Risk ratio | | Indirect comparison of Bijuva versus Estrogel (95% CI) |
|---|---|---|---|---|
| **Bijuva** | **Estrogel** | **Bijuva vs placebo** | **Estrogel vs placebo** | |
| **TEAE** | | | | |
| 1 mg E2 / 100 mg MP | 1.25 g/day | 1.4 | 1.1 | 1.2 (1.0,1.6) |
| 1 mg E2 / 100 mg MP | 2.5 g/day | 1.4 | 1.2 | 1.2 (1.0,1.5) |
| **Treatment-related TEAE** | | | | |
| 1 mg E2 / 100 mg MP | 1.25 g/day | 2.3 | 1.2 | **2.0 (1.1,3.6)** |
| 1 mg E2 / 100 mg MP | 2.5 g/day | 2.3 | 1.5 | 1.5 (0.9,2.7) |

Source: Table 2-40, p137 of the of the submission main body.
CI = confidence interval; E2 = 17β-estradiol; MP = micronised progesterone; TEAE = treatment emergent adverse event
**Bold** indicates statistically significant results

6.50 The ITC results showed no significant differences between Bijuva and Estrogel 2.5 g in TEAEs and treatment-related TEAEs, noting the limitations in such comparison, which included different study reporting periods (12 months in REPLENISH and 12 weeks in Archer et al. 2003), patient eligibility criteria (safety population was analysed in REPLENISH, whereas all patients were considered in safety analysis in Archer et al., 2003), and treatment composition (oral estradiol plus progesterone in Bijuva, versus transdermal estradiol alone in Estrogel). The ITC was conducted against Estrogel, due to lack of evidence for Estrogel Pro (the nominated comparator). The PSCR stated that the 12 month reporting period in the REPLENISH study is an advantage in establishing the safety profile for Bijuva over an extended period.

6.51 The ESC considered it was unknown what the long term effects of treatment are, given the shorter reporting periods for the trials used.

6.52 As discussed in paragraph 5.2, oral estrogen carries a higher risk of VTE than transdermal estrogen; however, the submission did not provide any evidence regarding the risk of VTE with Bijuva (oral estradiol) compared to Estrogel Pro (transdermal estradiol). A meta-analysis by Mohammed et al (2015)[15] reported that oral estrogen was associated with an increased risk of VTE (relative risk [RR]=1.63, 95% CI: 1.4, 1.9), compared to transdermal estrogen. Vinogradova et al. (2019)[16], a retrospective analysis with approximately 80,000 women in the UK, reported that oral estrogen therapy was associated with a significantly increased risk for VTE (adjusted odds ratio [OR]=1.6, 95% CI: 1.5, 1.6), and this increased risk remained significant for combined oral estrogen + progestogen (adjusted OR=1.7, 95% CI: 1.7,1.8) compared with no exposure. Vinogradova et al. (2019) concluded that in the present study, transdermal treatment was the safest type of MHT when risk of VTE was assessed.

[15] Mohammed, K., Abu Dabrh, A.M., et al. (2015), 'Oral vs Transdermal Estrogen Therapy and Vascular Events: A Systematic Review and Meta-Analysis', J Clin Endocrinol Metab, 100(11):4012-20. doi: 10.1210/jc.2015-2237.
[16] Vinogradova Y., Coupland C., et al. (2019), 'Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases', BMJ, 364:k4810 doi:10.1136/bmj.k4810

## *Benefits/harms*

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

## *Clinical claim*

6.54 The submission described Bijuva as non-inferior to Estrogel Pro in terms of effectiveness at improving estrogen-deficiency menopause symptoms and that both products provided comparable protection against endometrial hyperplasia. This claim was uncertain for the following reasons:

- The comparison was based on an unadjusted anchored ITC of Bijuva versus Estrogel (for VMS), using placebo as a common comparator, and an unadjusted unanchored ITC of Bijuva versus Estrogel Pro (for endometrial hyperplasia).
- The Bijuva trial (REPLENISH), Estrogel study (Archer et al. 2003), and Estrogel Pro study (Pélissier et al. 2001) had differences in study population, designs, durations, and outcome measures (for further details refer paragraph 6.43).
- No pre-specified non-inferiority margins were provided to formally test efficacy and safety claims.

6.55 The PSCR argued that it was not possible to provide pre-specified non-inferiority margins to formally test efficacy and safety outcomes, and that these are rarely available for safety claims. There is limited published information available on acceptable non-inferiority margins for VMS outcomes.

6.56 The submission described Bijuva as non-inferior to Estrogel Pro in terms of safety on the estrogen-associated AEs. This claim was uncertain because:

- There was a lack of head-to-head comparative AE data of Bijuva versus Estrogel Pro.
- The presented ITC of Bijuva versus Estrogel (not Estrogel Pro) on AE profile was based on studies with different reporting periods (12 months in REPLENISH and 12 weeks in Archer et al. 2003).
- No evidence was presented on the comparative risk of VTE and breast cancer of Bijuva versus Estrogel Pro, to assess the risk of VTE of oral versus transdermal estradiol, and the risk of breast cancer of continuous combined MHT versus cyclical MHT, noting that Estrogel Pro has both cyclical and continuous regimens.
- External evidence (Mohammed et al. 2015[13] and Vinogradova et al. 2019[14]) consistently suggests that oral estradiol is associated with a higher risk of VTE, compared to transdermal estradiol (for further details refer paragraph 6.52).
- Continuous combined MHT such as Bijuva may be associated with a higher breast cancer risk, compared to cyclical MHT such as Estrogel Pro (for further details refer paragraph 6.48).

6.57 The PSCR and pre-PBAC response claimed that the use of an anchored, naïve ITC for the submission was generally consistent with the methodology used for the consideration of Estrogel Pro by the PBAC. The PSCR and pre-PBAC response claimed that a more rigorous approach was taken in this submission, as a formal ITC was conducted and reported for Bijuva versus Estrogel Pro, which demonstrated comparable efficacy and safety, and the two patient populations were broadly similar.

6.58 The ESC considered the clinical claim was reasonable but uncertain, due to smaller, older studies being used, no head-to-head comparisons, and a lack of non-inferiority margins.

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

6.60 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

## *Economic analysis*

6.61 The submission presented a cost-minimisation approach (CMA) of Bijuva versus Estrogel Pro, based on the assumption that Estrogel Pro is the product that will most likely be displaced in clinical practice. As stated in paragraph 5.2, estradiol gel may not be an appropriate comparator for estradiol oral tablets.

6.62 For the requested population, i.e., postmenopausal women with an intact uterus experiencing estrogen deficiency symptoms, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: oral combination MHT, such as concomitant PBS-listed oral estradiol tablets and MP capsules. The PSCR argued that oral estradiol tablets + MP capsules was an inappropriate comparator as it would require patients to make two co-payments for two different medicines, reducing the financial benefits for patients from a fixed dose combination therapy listed on the PBS. The PSCR stated that Recommendation 18 from the Senate inquiry recommended that MHT products should be made more affordable to patients. The PSCR further claimed that taking one capsule would be preferred by patients rather than taking two separate capsules/tablets. The ESC noted that no data was provided in the PSCR to support or refute this claim, or whether this would influence uptake or adherence.

6.63 In the context of the cost-minimisation approach taken by the submission, a further consideration for the PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

6.64 The submission claimed that one capsule of Bijuva containing 1 mg of estradiol (oral) together with 100 mg of MP daily for 28 days is equi-effective to 1.5 mg of estradiol (two pumps of Estrogel) with 100 mg of MP daily for 30 days with Estrogel Pro.

6.65 The CMA assumed each pack of Bijuva provides 28 days of therapy, which was appropriate given it is a fixed-dose combination of estradiol and MP supplied in 28-capsule packs, with a recommended dose of 1 capsule daily. In contrast, the estimated 30 days of therapy with each pack of Estrogel Pro may be inaccurate:

- For the estradiol component of Estrogel Pro, most patients require two pumps of Estrogel daily (containing 1.5 mg of estradiol). Given that each pack contains 64 pumps of Estrogel, a single pack would provide up to 32 days of therapy. The submission further stated that being a pumped gel there is greater potential for wastage compared with a strictly metered dose, such as tablets or capsules, and greater potential for dosage creep. While one pack of Estrogel lasting 32 days is consistent with the duration used in the consideration of Estrogel (paragraph 6.119, estradiol and progesterone, PSD, November 2024 PBAC meeting), some women may respond to 1 pump (1.25 g) daily, in which case a pack would last longer than 32 days.
- For the MP component of Estrogel Pro, each pack contains 30 capsules, with most patients advised to take one capsule daily, providing up to 30 days of therapy. However, this assumption was not consistent with the recommended dosing regimens, or the approach adopted in the submission for MP (paragraph 6.120, estradiol and progesterone, PSD, November 2024 PBAC meeting). According to the Australian Menopause Society guidelines[17], MP is recommended as either continuous dosing (100 mg daily for 25 days of a 28-day cycle) or cyclical dosing (200 mg daily for 12 days of 28-day cycle) and may be given daily if adherence is an issue.
- Assuming 32 days with estradiol, the Estrogel Pro pack would provide up to 32 days of treatment, with a small wastage of MP. This estimate contrasts with the 30-day treatment per pack proposed in the submission, but was consistent with the duration of treatment per pack used in the consideration of Estrogel Pro (paragraph 6.121, estradiol and progesterone, PSD, November 2024 PBAC meeting).

6.66 The PSCR argued that as Estrogel contains 64 pumps of gel and most patients require 2 pumps daily, each pack of Estrogel Pro is expected to provide a maximum of 32 days of therapy. As the gel is measured with a pump device, there is greater potential for wastage and dosage creep compared to a capsule which has a strictly metered dose. The PSCR also argued that the Prometrium component provides a maximum of 30 days of therapy as there are 30 capsules in a pack.

6.67 The ESC noted that the dose of Estrogel is titrated to its effective dose, which can range from 1 pump daily (with one pack lasting 64 days, approximately 2 months) to 4 pumps daily (with one pack lasting approximately 16 days, approximately 2 weeks). The ESC advised that there may not be wastage of MP in practice, as patients may

[17]Australian Menopause Society (2023, October). AMS Guide to MHT/HRT Doses. Retrieved from https://menopause.org.au/hp/information-sheets/ams-guide-to-mht-hrt-doses

'carry over' remaining MP capsules to the next cycle. However, as Estrogel Pro was only listed on the PBS in March 2025, there is a lack of data on how long one dispensing of Estrogel Pro on the PBS lasts on average.

6.68 The CMA was conducted over a two-year time horizon without discounting to estimate the cost-minimised AEMP for Bijuva (Table 9). The resulting AEMP remained unchanged when recalculated over a one-year treatment period.

**Table 9: Results of the cost-minimisation approach**

| Component | Bijuva | Estrogel Pro |
|---|---|---|
| AEMP per pack | $39.28 | $42.09 |
| Days of coverage per prescription | 28 days | 30 days |
| Number of scripts over 2 years | 26.07 | 24.33 |
| Total cost of 2 years of treatment (based on AEMP) | $1,024.19 | $1,024.19 |

Source: Table 3-2, p150 of the submission main body.
AEMP = approved ex-manufacturer price.

6.69 The submission calculated the approved ex-manufacturer price (AEMP) of $39.28 for Bijuva based on the AEMP of Estrogel Pro. The submission requested a DPMQ of $55.69 for 1-pack of Bijuva 28 capsules, and $97.93 for the 2-pack (i.e., 60-day maximum dispensed quantity listing). However, the mark-ups, administration and handling fee, and dispensing fees were updated since July 2025, resulting in a corresponding DPMQ of $56.02 for 1-pack and $98.26 for the 2-pack.

6.70 As stated in paragraph 6.65, the treatment duration in the submission for a pack of Estrogel Pro was underestimated, and inconsistent with the treatment duration used in the November 2024 PBAC consideration of Estrogel Pro. Assuming a pack of Estrogel Pro provides a treatment duration of 32 days, the cost-minimised AEMP for Bijuva decreases by 6%, from $39.28 to $36.83. Based on the revised AEMP for Bijuva, the revised DPMQ was calculated as $53.39 for 1-pack of Bijuva and $93.00 for the 2-pack (i.e., 60-day maximum dispensed quantity listing).

6.71 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with Bijuva would be no more than the cost per patient of appropriate comparators. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

### *Drug cost/patient/year: $696.45*

6.72 Bijuva (a single fixed dose capsule containing both estradiol and MP) with 28 capsules per pack, provides 28 days of therapy. Based on the proposed DPMQ of $56.02, the estimated cost per patient per year of treatment with Bijuva was $730.76 ($56.02 x [365.25/28]). Based on the revised DPMQ of $53.39, as described in paragraph 6.70, the estimated cost per patient per year of treatment with Bijuva was $696.45 ($53.39 x [365.25/28]).

6.73 For Estrogel Pro, the duration of treatment was 32 days based on the individual component of Estrogel in the pack. Based on the published DPMQ of $59.05, the

estimated cost per patient per year of treatment with Estrogel Pro was $674 ($59.05 x [365.25/32] days), with a small amount of wastage associated with MP.

## *Estimated PBS usage & financial implications*

6.74 This submission was not considered by DUSC.

6.75 The submission used a combined abridged epidemiological approach and market share approach to estimate the use and financial impact of listing Bijuva on the PBS. The sources of data used in the financial estimates are presented in Table 10, outlining the key inputs relied on in the financial estimates.

**Table 10: Key inputs for financial estimates**

| Parameter | Value applied and source | Comment* |
|---|---|---|
| Number of patients | [redacted][1] in Year 1, increasing to [redacted][2] in Year 5 (patient numbers for Year 6 not included, however number of scripts for Year 6 is included [see below]). Based on the patient range data reported in the PSD for estradiol and progesterone from the November 2024 PBAC meeting. | This was uncertain, as estimates were based on ranges in the estradiol and progesterone PSD, and not exact numbers. Additionally, these patient numbers were based on the private market of Estrogel Pro, and no evidence was provided to support the assumption in market growth rate (paragraph 6.136, estradiol and progesterone PSD, November 2024 PBAC meeting). The number of prescriptions per year was based on a 32-day treatment duration per Estrogel Pro pack, which does not align with the 30-day duration assumed in the CMA.<br><br>Furthermore, the additional 30% growth adjustment likely overestimated utilisation compared to the 2024 iQvia sales data for Estrogel Pro. |
| Total number of prescriptions for Estrogel Pro | [redacted][3] in Year 1, increasing to [redacted][4] in Year 6. Derived by multiplying the estimated number of patients by the annual number of prescriptions per patient for Estrogel Pro (11.41), then adjusted by 30% to account for uncertainty, as noted by the ESC in the estradiol and progesterone PSD from the November 2024 PBAC meeting. | |
| Uptake rate | [redacted]% in Year 1 increasing to [redacted]% in Year 6. Based on sponsor's assumption. | This was uncertain and is not supported by any evidence. Bijuva may substitute for other PBS-listed MHTs, particularly oral MHTs including Femoston. |
| Substitution rate | 1 x Estrogel Pro prescription is equivalent to 1.07 x Bijuva prescriptions. Based on duration of therapy of 30 days for Estrogel Pro and 28 days for Bijuva. | While this was consistent with the assumption used in the submission's CMA, Estrogel Pro provides 32 days of therapy (paragraph 6.65). |
| % of use in postmenopausal women | 85.3%. Derived from Worsley R., et al. (2016)[18] based on the assumption that Estrogel Pro may be used for both perimenopausal and postmenopausal women due to transdermal estrogel, whereas Bijuva is indicated for postmenopausal use only. | This was not appropriate given the TGA indication for Estrogel Pro is similar to Bijuva. |
| % of prescriptions dispensed as part of 60-day MDQ | 27%. Based on number of services PBS item numbers 14721T and 14720R for Estrogel Pro from March – April 2025. | This may be reasonable, however as this is only based on 2 months' of services for Estrogel Pro, the proportion of prescriptions dispensed as 60-Day MDQ may change with a longer duration of listing. |
| **Costs** | | |
| Bijuva | $55.69 for 30-day and $97.93 for 60-day. Based on requested DPMQ. | The DPMQs were revised during the evaluation as the mark-up fees for drugs was updated on July 2025, resulting in a DPMQ of $56.02 for 30-day and $98.26 for 60-day. |
| Estrogel Pro | $58.72 for 30-day and $103.99 for 60-day. Based on published DPMQ for PBS item number 14721T and 14720R (Estrogel Pro). | The DPMQs were revised during the evaluation as the mark-up fees for drugs was updated in July 2025, resulting in a DPMQ of $59.05 for 30-day and $104.32 for 60-day maximum dispensed quantity. |
| Patient copayment | PBS: $29.07 and RPBS: $7.46. Based on a distribution of 99.79% PBS and 0.21% RPBS, as per PBS item number 14721T and 14720R (Estrogel Pro). | This was reasonable. |

Source: Table 4-2, p156; Table 4-3, p156; Table 4-4, p158, Table 4-6, p160 and Section 4.2.3, pp160-161 of the submission main body.
*Added during evaluation
CMA = cost-minimisation approach; DPMQ = Dispensed price for maximum quantity; ESC = Economics Sub-Committee; MDQ = maximum dispensed quantity; MHT = menopausal hormone therapy; MP = micronised progesterone; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme; TGA = Therapeutic Goods Administration.
*The redacted values correspond to the following ranges:*

[1] *50,000 to < 60,000*
[2] *60,000 to < 70,000*
[3] *700,000 to < 800,000*
[4] *1,000,000 to < 2,000,000*

6.76 Table 11 presents the estimated financial implications of listing Bijuva.

**Table 11: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | | |
| Total prescription numbers – Bijuva | [redacted][1] | [redacted][2] | [redacted][3] | [redacted][4] | [redacted][5] | [redacted][5] |
| **Estimated financial implications of Bijuva** | | | | | | |
| Cost to PBS/RPBS less copayments* | $[redacted][6] | $[redacted][6] | $[redacted][6] | $[redacted][6] | $[redacted][6] | $[redacted][6] |
| **Estimated financial implications for Estrogel Pro** | | | | | | |
| Cost to PBS/RPBS less copayments* | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] |
| **Net financial implications** | | | | | | |
| Net cost to PBS/RPBS* | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] | -$[redacted][6] |

Source: Table 4-13, p164 of the submission main body.
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
*corrected during evaluation by using updated mark-up fees for drugs as of July 2025.
*The redacted values correspond to the following ranges:*
[1] *20,000 to < 30,000*
[2] *40,000 to < 50,000*
[3] *60,000 to < 70,000*
[4] *80,000 to < 90,000*
[5] *100,000 to < 200,000*
[6] *$0 to < $10 million*

6.77 The total saving to the PBS/RPBS of listing Bijuva was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing.

6.78 The submission estimated listing Bijuva on the PBS would result in a cost saving, due to the higher number of patient co-payments as 1 pack of Bijuva provides fewer days of therapy compared to 1 pack of Estrogel Pro (paragraph 6.65).

6.79 The total savings to the PBS/RPBS of listing Bijuva were likely overestimated due to following reasons:

- The submission assumed that Bijuva would only substitute for Estrogel Pro, and did not account for patients using other forms for MHT (both PBS and non-PBS listed) who may switch to using Bijuva if PBS-listed.
- The key inputs for Estrogel Pro (e.g. the number of patients and prescriptions) were uncertain as they were based on utilisation of Estrogel Pro in the private market and adjusted by 30% to account for uncertainty.
- Furthermore, the number of prescriptions per year was calculated assuming a 32-day treatment duration per pack, which is inconsistent with the 30-day duration used in the CMA.

[18] Worsley, R., et al., 2016, 'Low use of effective and safe therapies for moderate to severe menopausal symptoms: a cross-sectional community study of Australian women', Menopause 23 (1): 11–7, https://doi.org/10.1097/gme.0000000000000495.

6.80 The PSCR argued that it was irrelevant to include non-PBS listed forms of MHT that may be substituted for Bijuva in the financial estimates, as these medicines are not Government subsidised. The PSCR claimed that the financial estimates for Estrogel Pro already account for patients using non-PBS subsidised medicines who may switch to medicines newly listed on the PBS, and the listing of Bijuva is unlikely to meaningfully impact this trend. The PSCR claimed that estradiol valerate listed on the PBS is different to the estradiol in Bijuva, and that Femoston that is PBS-listed contains synthetic dydrogesterone and uses a cyclical dosing regimen, therefore these are not appropriate alternatives to Bijuva.

6.81 The ESC considered the financial estimates and inputs were uncertain. The ESC advised that patients currently using other MHT products who may switch to Bijuva if PBS-listed should be included in the financial estimates, especially in light of MHT shortages, and noted that some patients may prefer using an oral rather than topical medicine. The ESC advised that as Estrogel Pro is currently PBS-listed, the financial estimates should incorporate utilisation data of Estrogel Pro since its listing on the PBS.

6.82 The ESC advised that in practice patients using MHT patches may switch to an oral formulation of MHT such as Bijuva if they were unable to tolerate topical application. The ESC considered patients were more likely to switch from a topical MHT patch to an oral formulation, rather than switching to a topical gel (such as Estrogel Pro).

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

# 7 PBAC Outcome

7.1 The PBAC recommended the listing of estradiol with progesterone (Bijuva) as a General Schedule unrestricted benefit listing, and a corresponding General Schedule restricted benefit listing for 60-day maximum dispensed quantity.

7.2 The PBAC noted this product is currently available on the private market, however cost is a barrier to access. The PBAC noted consumer input stated that it was important to have a range of MHT options available on the PBS, particularly in the context of shortages of other MHT products. The PBAC noted comments that PBS listing of Bijuva would support equitable access to a range of MHT options, particularly for individuals who require MHT but where transdermal or synthetic hormones are not appropriate or not preferred, and that a combination capsule presentation offers convenience. The PBAC noted that a prescription for estradiol with progesterone would reduce co-payments and out-of-pocket expenses compared to oral estradiol and progesterone prescribed separately.

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.

7.4 The PBAC advised that there is a need to maintain a diverse range of MHT options on

the PBS. The PBAC noted that there is currently no oral fixed dose combination product containing estradiol and progesterone (or a progestogen) for continuous MHT listed on the PBS, however, estradiol and progesterone (or a progestogen) are available separately. The PBAC noted that there are also MHT products that combine topical estradiol and oral progesterone or a topical progestogen available on the PBS that can be used as continuous MHT. It is generally accepted that transdermal estradiol has a lower risk of VTE than oral estradiol.

7.5 The PBAC advised that the claim of non-inferior efficacy for Bjiuva against Estrogel Pro was adequately supported by the evidence provided. The PBAC also advised that there is currently no evidence that any estradiol is more bioidentical or provides an added benefit over another. The PBAC noted that evidence was provided comparing the incidence of endometrial hyperplasia and bleeding, however no evidence was provided regarding the risk of VTE with Bijuva compared to Estrogel pro. The PBAC advised that current evidence indicates that oral estradiol increases the risk of VTE compared to transdermal estradiol. The PBAC advised the claim of non-inferior safety against Estrogel Pro was not adequately supported.

7.6 The PBAC noted that the main basis for the choice of Estrogel Pro (estradiol (as hemihydrate) 0.06% transdermal gel with progesterone 100 mg capsule) as the comparator was that it was the only combination bioidentical MHT that contained the same active ingredients as Bijuva listed on the PBS. The PBAC recalled from its November 2024 consideration of estradiol and progesterone that oral estradiol tablets were previously considered to be inappropriate comparators for transdermal estradiol gels (paragraph 5.2, estradiol and progesterone, Public Summary Document [PSD], November 2024 PBAC Meeting).

7.7 The PBAC advised that although there is a need to maintain a range of MHT options on the PBS, insufficient evidence was provided to justify a price premium for Bijuva, as a fixed dose combination product, over the sum of the individual prices of an existing oral estradiol product and progesterone. The PBAC advised that oral estradiol and progesterone would be a more appropriate comparator. The PBAC advised that listing should be on a cost minimisation basis against estradiol valerate 1 mg tablet (28 days) and progesterone 100 mg capsule (25 days out of a 28-day cycle). The PBAC advised that Bijuva, i.e. estradiol 1mg with progesterone 100 mg, is equi-effective to 1 mg estradiol valerate and progesterone 100 mg.

7.8 The PBAC noted that the financial estimates only accounted for substitution of Bijuva for Estrogel Pro and did not include other MHT products. The PBAC advised that it was likely that Bjiuva would also substitute for other less expensive oral estradiol and progesterone (and progestogen) products that are prescribed separately. The PBAC noted where Bijuva substituted for two individual products, that a reduction in the number of patient co-payments would also impact the financial estimates. The PBAC advised that patients prescribed MHT patches, which are less costly, may also switch to Bijuva. The PBAC advised that the cost saving proposed was likely overestimated.

7.9 The PBAC advised that Bijvua was suitable for prescribing by nurse practitioners, for

initial and continuing therapy.

7.10 The PBAC advise that Continued Dispensing arrangements should not apply for Bijuva.

7.11 The PBAC advised that Bijuva should not be exempt from the Early Supply Rule as it currently applies to Estrogel Pro and other PBS-listed MHT medicines.

7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Bijuva is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over estradiol (as valerate) 2 mg tablet and progesterone 100 mg capsule, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.13 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

**Outcome:**
Recommended

# 8 Recommended listing

8.1 Add new item:

**30-day listing**

| **MEDICINAL PRODUCT medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|---|
| ESTRADIOL + PROGESTERONE | | | | | |
| estradiol 1 mg + progesterone 100 mg capsule, 28 | NEW MP NP | 1 | 28 | 5 | Bijuva |
| | | | | | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) | | | | |
| | **Prescriber type:** ☒Medical Practitioners ☒Nurse practitioners | | | | |
| | **Restriction type:** ☒unrestricted benefit | | | | |

**60-day listing**

| **MEDICINAL PRODUCT medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|---|
| ESTRADIOL + PROGESTERONE | | | | | |
| estradiol 1 mg + progesterone 100 mg capsule, 28 | NEW MP NP | 2 | 56 | 5 | Bijuva |
| | | | | | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** ☒ GENERAL - General Schedule (Code GE) | | | | |
| | **Prescriber type:** ☒Medical Practitioners ☒Nurse practitioners | | | | |
| | **Restriction type:** ☒ Restricted benefit | | | | |
| | **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 restriction the sponsor will be informed.***

# 9 Context for Decision

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

# 10 Sponsor's Comment

The sponsor had no comment.