5.14 TESTOSTERONE
Transdermal cream 10 mg per mL, 50 mL, AndroFeme 1®, Lawley Pharmaceuticals Pty Ltd.

1 Purpose of submission

1.1 The Category 1 submission requested Restricted Benefit listing for testosterone 1% cream for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women.

1.2 Listing was requested on the basis of a cost comparison with the currently PBS listed topical testosterone product (AndroForte 5, 50 mL tube) (Table 1). The clinical comparison presented was versus placebo.

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

Component	Description
Population	Female patients that are postmenopausal (either naturally or surgically) with hypoactive sexual desire dysfunction (HSDD) that has failed to be treated by appropriate education and correction of modifiable biopsychosocial factors (which may include neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress or specific cultural or religious beliefs), according to the International Society for the Study of Women's Sexual Health (ISSWSH) process of care (Clayton, Goldstein et al. 2018).
Intervention	Testosterone cream 1% w/v (10 mg/mL), 50 mL cream tube. The recommended starting dose is 5mg once daily applied to the upper outer thigh or buttock.
Comparator	Placebo
Outcomes	Outcomes include change in Brief Index of Sexual Functioning for Women (BISF-W) score, change in the Depression, Anxiety and Stress Scale (DASS) score, change in Profile of Mood States (POMS), change in Total Sexual Function Score and safety.
Clinical claim	In the treatment of postmenopausal women with HSDD, 1% testosterone cream is superior to placebo in terms of efficacy, and non-inferior in terms of safety.

Source: Table 1.1, p12 of the submission.

2 Background

Registration status

2.1 Testosterone 1% cream was TGA registered on 23 November 2020 for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women.

2.2 The sponsor has manufactured testosterone as a 1% cream since 1999 and supplied the cream via mail order[1] under Section 6 of the Therapeutic Goods Act 1989 from pharmacies in Western Australia until the time of registration. The sponsor estimated

[1] Section 6 of the Therapeutic Goods Act 1989 provides for exemptions of therapeutic goods produced by natural persons (sole traders) from being included on the ARTG upon introduction of the Act.

that this has resulted in an estimated 95,037 patient-years of exposure and that this demonstrated clinician familiarity and genuine clinical need.

Previous PBAC consideration

2.3 There has been no previous PBAC consideration of testosterone 1% cream for HSDD in postmenopausal women and no other products are PBS-listed for this indication.

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

3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

30-day listing

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
TESTOSTERONE					
~~testosterone 1.0% w/v cream (10mg/ml), 50Ml~~ testosterone 1% (10 mg/mL) cream, 50 mL	NEW MP NP	1	1	1	AndroFeme 1

Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒ Restricted benefit
Prescribing rule level:	
Administrative advice: *No increase in the maximum number of repeats may be authorised.*	
Restriction Summary [new1] / Treatment of Concept: [new1A]	
Indication: Hypoactive Sexual Desire Dysfunction (HSDD) *in postmenopausal women*	
~~**Treatment Phase:** All~~	
Clinical criteria:	
~~Patients must have failed to be treated by appropriate education and correction of modifiable biopsychosocial factors (which may include neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress or specific cultural or religious beliefs), according to the International Society for the Study of Women's Sexual Health (ISSWSH) process of care.~~ *The condition must have failed to be treated by either (i) appropriate education; (ii) correction of modifiable biopsychosocial factors according to the International Society for the Study of Women's Sexual Health (ISSWSH) process of care.*	
AND	
Clinical criteria:	
Patient must not be contraindicated to testosterone therapy. ~~(e.g. serum testosterone high, history of breast cancer, high risk of CVD, high risk of VTE, significant liver disease, professional singer)~~	
~~**Treatment criteria:**~~	
~~Must be treated by a medical practitioner;~~	
~~OR~~	
~~Must be treated by a nurse practitioner~~	

Population criteria:
~~Patient must be aged 18 years or older;~~ *Patient must be at least 18 years of age*
AND
Population criteria:
~~Patient must be considered naturally postmenopausal;~~
~~OR~~
~~Patient must be considered surgically postmenopausal.~~
Patient must be postmenopausal either (i) naturally, (ii) surgically
Prescribing Instructions: *Correction of modifiable biopsychosocial factors may include but not limited to neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress or specific cultural or religious beliefs.*
Prescribing Instructions: *Prescribers must ensure that the serum concentration of total testosterone of their patient is maintained within the approximate physiological range for premenopausal women. Prescribers must follow the dosing regimen and monitoring requirements as per the Therapeutic Goods Administration (TGA) approved Product information.* ~~patient should have a follow-up blood test taken three to six weeks after initiating treatment. Optimally, the serum concentration of total testosterone should be maintained within the approximate physiological range for premenopausal women.~~ ~~If no improvement in symptoms is seen within 3 months and if the testosterone concentration is within the premenopausal reference range a dose increase up to 10 mg testosterone (1.0 mL) daily can be used with follow up clinical and biochemical monitoring. This dose should only rarely be exceeded. If there is no improvement in symptoms after 6 months of continuous therapy, treatment should be discontinued and alternative options be considered.~~

60-day listing

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
TESTOSTERONE					
~~testosterone 1.0% w/v cream (10mg/ml), 50Ml~~ testosterone 1% (10 mg/mL) cream, 50 mL	NEW MP NP	2	2	1	AndroFeme 1
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners					
Restriction type: ☒ Restricted benefit					
Prescribing rule level:					
Administrative advice: *No increase in the maximum number of repeats may be authorised.*					
Restriction Summary [new2] / Treatment of Concept: [new2A]					
Indication: Hypoactive Sexual Desire Dysfunction (HSDD) *in postmenopausal women*					
Clinical criteria:					
The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient,					
AND					
Clinical criteria:					

~~Patients must have failed to be treated by appropriate education and correction of modifiable biopsychosocial factors (which may include neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress or specific cultural or religious beliefs), according to the International Society for the Study of Women's Sexual Health (ISSWSH) process of care.~~ *The condition must have failed to be treated by either (i) appropriate education; (ii) correction of modifiable biopsychosocial factors according to the International Society for the Study of Women's Sexual Health (ISSWSH) process of care.*
AND
Clinical criteria:
Patient must not be contraindicated to testosterone therapy. ~~(e.g. serum testosterone high, history of breast cancer, high risk of CVD, high risk of VTE, significant liver disease, professional singer)~~
~~**Treatment criteria:**~~
~~Must be treated by a medical practitioner;~~
~~OR~~
~~Must be treated by a nurse practitioner~~
Population criteria:
~~Patient must be aged 18 years or older;~~ *Patient must be at least 18 years of age*
AND
Population criteria:
~~Patient must be considered naturally postmenopausal;~~
~~OR~~
~~Patient must be considered surgically postmenopausal.~~
Patient must be postmenopausal either (i) naturally, (ii) surgically
Prescribing Instructions: *Correction of modifiable biopsychosocial factors may include but not limited to neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress or specific cultural or religious beliefs.*
Prescribing Instructions: *Prescribers must ensure that the serum concentration of total testosterone of their patient is maintained within the approximate physiological range for premenopausal women. Prescribers must follow the dosing regimen and monitoring requirements according to the Therapeutic Goods Administration (TGA) approved Product information.* ~~patient should have a follow up blood test taken three to six weeks after initiating treatment. Optimally, the serum concentration of total testosterone should be maintained within the approximate physiological range for premenopausal women.~~ ~~If no improvement in symptoms is seen within 3 months and if the testosterone concentration is within the premenopausal reference range a dose increase up to 10 mg testosterone (1.0 mL) daily can be used with follow up clinical and biochemical monitoring. This dose should only rarely be exceeded. If there is no improvement in symptoms after 6 months of continuous therapy, treatment should be discontinued and alternative options be considered.~~

3.2 The topical testosterone products currently listed on the PBS are Authority Required and must be prescribed by or in consultation with a non-GP specialist. Conversely, the proposed restriction for HSDD in postmenopausal women is for a Restricted Benefit and does not require a non-GP specialist practitioner; rather it requests prescription by a medical or nurse practitioner (consistent with other postmenopausal management, which is predominantly undertaken in primary care).

3.3 The submission referred to the Senate Committee report on 'Issues related to menopause and perimenopause' September 2024[2], which refers to testosterone. Specifically, recommendation 4.78 and 4.79 state:

> 4.78 Testosterone can also be used for women experiencing negative impacts of perimenopause and menopause on their libido.
>
> 4.79 A number of practitioners emphasised the 'gold standard' of combined MHT [menopausal hormone therapy] which include body identical transdermal estradiol, oral micronized progesterone and inclusion of testosterone where needed as preferable because of their lower risk profile.

3.4 The indication requested by the submission is for treatment of HSDD, which is not the same as low libido and is not an effect of menopause. Use in women in perimenopause for any indication would not be consistent with the proposed restriction.

3.5 Use in women experiencing negative impacts of menopause on their libido (recommendation 4.78) is not aligned with the restrictions for PBS-subsidised use of testosterone in men. The restrictions for the existing PBS-listed testosterone products do not allow for use in men who have low libido caused by ageing only. Use in men (without an established pituitary or testicular disorder) requires establishing androgen deficiency by biochemical evaluation on at least two separate morning blood samples (requiring a plasma testosterone level of less than 6 nmol/L, or 6-15 nmol/L with high luteinising hormone levels). The ESC considered that it could be appropriate to strengthen the requirements for monitoring of testosterone levels in the proposed restriction to ensure they remain within appropriate physiological levels.

3.6 The evaluation considered that there is a high likelihood of extensive use outside the restriction, including in premenopausal women, or those with reduced libido and no personal distress. In their Pre-Sub-Committee Response (PSCR), the Sponsor stated that they did not support an Authority Required listing. The PSCR stated that "a surge of prescribing to premenopausal women is unlikely because the product is licensed expressly for postmenopausal women" and that tight diagnostic entry criteria for female HSDD would be adhered to.

3.7 The requested restriction specified in a Prescribing Instruction that "The patient should have a follow-up blood test taken three to six weeks after initiating treatment." However, the restriction does not explicitly state that the patient should have a baseline testosterone measurement, as recommended in the PI for testosterone 1% cream. The ESC considered it reasonable that testosterone should be tested at: baseline, 3-6 weeks after initiating treatment, at 12 weeks ("full assessment"), and then 6-monthly.

[2] Available at: Issues related to menopause and perimenopause – Parliament of Australia

3.8 The ESC noted that the submission had not suggested restricting use to specialist clinicians and as such, prescribing would be in primary care. The ESC agreed with the evaluation that there would be a high risk of use outside the restriction (in premenopausal women and in women who did not meet the clinical criteria). To ensure use would be aligned with the proposed patient population, the ESC considered the listing should be Authority Required and noted that HSDD can be defined in a variety of ways (see paragraph 4.2 below). The ESC considered that the proposed clinical criteria relating to diagnosis could be enhanced by including additional details in the restriction to direct clinicians to the International Society for the Study of Women's Sexual Health (ISSWSH) criteria.

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

4 Population and disease

4.1 HSDD is characterised by at least 6 months of persistent or recurrent lack of desire for sexual activity and significant personal distress as a result.

4.2 According to the ISSWSH (Parish, 2016), HSDD is lack of motivation for sexual activity as manifested by any of the following for a minimum of 6 months:

- Lack of motivation for sexual activity as manifested by:
  - Decreased or absent spontaneous desire (sexual thoughts or fantasies); or
  - Decreased or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity;
- Loss of desire to initiate or participate in sexual activity, including behavioural responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders;
- And is combined with clinically significant personal distress that includes frustration, grief, guilt, incompetence, loss, sadness, sorrow or worry.

4.3 The diagnosis of HSDD is not appropriate if a woman's lack of interest in sex is situational (e.g., due to conflict or dissatisfaction with a current partner), due to a sexual pain disorder, to physical or mental health conditions, or to medications (Clayton, 2018b). The diagnosis of HSDD is not appropriate if a woman is satisfied with her own level of sexual interest but distressed by conflict with her partner caused by discrepant levels of sexual interest. Because of the number and complexity of the issues that may underlie sexual dysfunction, diagnosis and management of HSDD are time-consuming and require high levels of expertise in multiple areas (Clayton, 2018b).

4.4 HSDD was one of seven forms of female sexual dysfunction (FSD) defined in DSM-4. DSM-5 merged HSDD with another of the FSDs in DSM-4, Female Sexual Arousal Disorder, to create Female Sexual Interest and Arousal Disorder (FSIAD). The term

HSDD has been retained by the ISSWSH and continues to be widely used (Parish, 2016).

4.5 A figure of 10% for the prevalence of HSDD is widely used; an Australian study estimated the prevalence to be 16% but noted that small changes in methodology could have large effects on estimated prevalence (Hayes, 2008).

4.6 Whether there is an effect of menopause on sexual function independent of age is controversial, but HSDD is not specifically related to menopause.[3] Sexual function in women, including the level of sexual desire, decreases with age, but distress caused by changes in sexual function also decreases with age, so that the prevalence of HSDD is not significantly higher in naturally postmenopausal women than in premenopausal women (Leiblum 2006, Dennerstein 2006). HSDD may be more prevalent in women who have undergone surgical menopause, but the data do not distinguish between the hormonal effects of surgical menopause and the effects of the condition which required surgery.

4.7 Testosterone levels in women peak at around the age of 20 years then decline steadily to about half the peak level at around age 40, after which they are stable.[4] Menopause is not associated with a decline in testosterone levels. Further, there is no evidence that the decrease in women's sexual function with age is related to the decline in testosterone levels over the reproductive years, or that deficiency of testosterone has any role in causation or severity of HSDD. For this reason, the evaluation considered that the submission's description of testosterone 1% cream used for HSDD as "hormone replacement therapy" is unjustified.

4.8 Application of exogenous testosterone causes a dose-dependent increase in sexual interest in both hypogonadal and eugonadal men and in transgender men - i.e., regardless of whether there is testosterone deficiency. For this reason, testosterone may benefit women with distress caused by low sexual interest, although testosterone deficiency does not appear to be the cause of the low sexual interest.

4.9 This applies equally to premenopausal and postmenopausal women. There have been two trials of testosterone in premenopausal women with low sexual desire, and one trial of testosterone in women taking selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) and low sexual desire in which 77% of patients were premenopausal.

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[3] Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? *Fertil Steril* 2001; 76:456-460.

[4] Handelsman DJ, Sikaris K, Lam PL. Estimating age-specific trends in circulating testosterone and sex hormone-binding globulin in males and females across the lifespan. *Ann Clin Biochem* 2015; 53:377-384.

- Goldstat (2003) reported strongly positive effects of testosterone treatment on sexual interest and satisfaction, and on well-being in 34 premenopausal women who had low libido but not necessarily HSDD.
- Davis et al studied three doses of testosterone in 261 premenopausal women with a decrease in satisfying sexual activity, finding increases in the frequency of satisfying sexual events that were similar to those seen in postmenopausal women but did not show a within-trial comparative benefit because the placebo response was larger than in postmenopausal women.[5]
- Fooladi (2014) enrolled 44 women taking SSRI or SNRI; the mean age was 48 and 77% were premenopausal; there was an increase in sexual interest and in the frequency of sexually satisfying events, but only the increase in the frequency of sexually satisfying events was statistically significant because the placebo response was large.

These trials were interpreted by the evaluation as unconvincing evidence of efficacy in premenopausal women, and use of testosterone in premenopausal women also carries a risk of adverse effects on the foetus in the event of pregnancy during treatment.

4.10 The proposed management algorithm in the submission places testosterone after the treatment of modifiable psychosocial factors and a trial of estrogen ± progestogen if there are symptoms of the genitourinary syndrome of menopause. The algorithm requires measurement of serum testosterone before treatment is initiated because it considers that a high normal level is a contraindication to testosterone treatment of HSDD (it is not stated, but this is presumably to minimise the risk of unwanted androgenic effects, since it is stated that the level of serum testosterone is not a diagnostic criterion for HSDD (paragraph 4.7)). The evaluation noted that this was not consistent with the proposed restriction because the restriction does not require serum testosterone to be tested before initiation, only 3-6 weeks after initiation.

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

5 Comparator

5.1 The submission nominated placebo as comparator. The evaluation considered that this was not appropriate; see paragraphs 5.4 to 5.7 below.

[5] Davis SR, Papalia MA, Norman RJ, et al. Safety and Efficacy of a Testosterone Metered-Dose Transdermal Spray for Treating Decreased Sexual Satisfaction in Premenopausal Women: A Randomized Trial. Ann Intern Med 2008; 148:569-577.

5.2 The following topical testosterone products are available on the PBS for men as Authority listings, requiring non-GP specialist treatment and prescription (or consultation with):

- Testosterone 5% (AndroForte 5®)
  - 50 mg/mL cream, 50 mL
- Testosterone 2% (Testavan®)
  - 23 mg/actuation gel, 56 actuations
- Testosterone 1% (Testogel®)
  - 12.5 mg/actuation gel, 2 × 60 actuations
  - 50 mg/5 g gel, 30 x 5 g sachets.

The PBS-listed indications are androgen deficiency, micropenis, induction of puberty, and constitutional delay of growth or puberty. The TGA indications for all the testosterone products are for testosterone replacement therapy for male hypogonadism.

5.3 The most recent PBAC consideration of topical testosterone was for testosterone cream 5% (AndroForte 5) in March 2021, when the sponsor requested a review of the price and equi-effective dosing. There is currently a price difference between AndroForte 5 and the two other topical testosterone products listed on the PBS, Testogel and Testavan. This is discussed further in paragraph 6.47.

5.4 The ESC noted that the Product Information for Testogel and Testavan specifically contraindicate use in women, and the Product Information for AndroForte 5 warns that it should not be used in women due to possible virilising effects. However, the submission acknowledged that testosterone that is indicated and marketed for the treatment of men can be and is used to treat women with HSDD.[6] The occurrence of this practice is supported by the global consensus statement presented by the submission as authoritative, which states that "Where an appropriate approved female testosterone preparation is not available, off-label prescribing of an approved male formulation is reasonable, provided hormone concentrations are maintained in the physiologic female range (Expert Opinion)" (Davis, Baber, 2019). This position statement was endorsed by the Endocrine Society of Australia and the Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG).

5.5 The evaluation considered that currently listed testosterone preparations being contraindicated (or not recommended) in women is not necessarily a reason they should not be comparators, because they are being used and will be replaced. The ESC noted that the PBAC Guidelines state: "Reference to the TGA-approved indications, to trial evidence, or to any other authority, would not usually constitute reasonable

[6] Section 3.3.2 on p99 quotes figures of 10%, 5% and 3% for the proportion of testosterone use by women in the age groups 41-45, 46-50 and 51-55 respectively, but conflates use by transgender men with use to treat HSDD.

grounds to exclude an unrestricted pharmacological analogue as a main comparator".[7] While the topical testosterone products available on the PBS do not have unrestricted PBS listings, women are accessing them with either a private script or off-label with a PBS prescription.

5.6 The submission justified the exclusion of existing testosterone preparations as comparators on the grounds that the lowest dose they are designed to deliver accurately is higher than the dose for women, and that this exposes women to unwanted androgenic effects. However, the only data presented were from the adverse event reporting system in the UK, where, from 2010 to 2024, 66 adverse events attributed to topical testosterone in women were reported; the greatest number reported in any year was 18, although "male-licensed testosterone is being prescribed to thousands of women each month".

5.7 For the reasons discussed in paragraphs 5.5 and 5.6, the evaluation and the ESC considered that the PBS-listed topical testosterone preparations, private prescription of other testosterone preparations, or compound testosterone preparations may be appropriate comparators.

5.8 The PSCR maintained that male testosterone products are not appropriate comparators or substitutes given that these products are specifically contraindicated (or in the case of AndroForte 5, not recommended) for use in women. The PSCR further stated that TGA registered male gels/solutions are formulated with potent permeation enhancers and solubility agents (e.g., isopropyl myristate + ethanol; oleic acid + isopropyl alcohol; diethylene glycol monoethyl ether/propylene glycol; pentadecalactone), producing powerful systemic uptake aimed at male targets that have been engineered to deliver much higher exposure than what women require. The PSCR stated that the female 1% cream is distinct from the male products in that it uses a cream base with almond oil (~70% oleic acid) and micronised testosterone dispersed in the vehicle, yielding moderate absorption. However, the Second Round Clinical Evaluation Report for testosterone 1% cream stated that “The Sponsor indicated that the new strength product has the same qualitative formulation as the currently registered product Androforte 5 and the composition has been modified to increase the purified water diluent content to account for the lower testosterone concentration”.

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

[7] PBAC, Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 5.0) Section 1.1.3, July 2016.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (368), health care professionals (80) and organisations (The Australian College of Nurse Practitioners (ACNP), the Australasian Menopause Society (AMS), RANZCOG, WellFemme Telehealth Menopause Clinic, Women's Health & Research Institute of Australia, Genspect Australia, Healthy Hormones, and the LGB Alliance Australia) via the Consumer Comments facility on the PBS website.

6.3 The comments from consumers and health care professionals described a range of benefits of treatment with testosterone 1% cream including improved energy levels, mood, self-esteem and quality of life, improved relationship health, improved libido, wellbeing, bone and muscle health, enhanced cognition, reduced fatigue, and the potential for deprescribing of antidepressants and antipsychotics. The PBAC noted that many of the benefits described were outside the scope of HSDD and that many consumers and health care professionals equated HSDD with low libido, having used the terms synonymously. The PBAC noted that the comments described issues related to gender inequity and prohibitive cost, as well as the potential for inappropriate use of testosterone when it is not indicated, and the risk of adverse effects. The PBAC noted several perimenopausal women stated they were using testosterone 1% cream, which highlighted that the therapy is currently being used outside its TGA approved indication. The PBAC noted that some health care professionals did not support listing of testosterone 1% cream on the PBS.

6.4 The PBAC noted that comments from AMS indicated that "the only evidence-based indication for the use of testosterone in women is for the treatment of HSDD" and that "other purported benefits reported in some social media outlets are without scientific basis". The PBAC noted that the AMS supported an Authority Required (streamlined) listing. Similarly, LGB Alliance Australia supported a listing for HSDD, however the PBAC noted that the organisation did not support use in premenopausal women or for any other indication, noting the absence of long-term safety data and that their support was in the context that robust safeguards should be used to avoid unintended use in younger populations that would expose them to "unassessed harm and the PBS to unplanned cost".

6.5 Genspect Australia inferred the submission sought to secure access through the "back door" of a HSDD listing, but that such a listing "would place younger cohorts at unknown and unassessed risk, particularly given the higher doses sought for masculinisation and other unapproved purposes" and that the proposed listing would "expose the PBS to significant financial risk from uncontrolled off-label use". Genspect

Australia also noted that that the requested listing is much broader than the restrictions for male testosterone products.

6.6 WellFemme Telehealth Menopause Clinic and Healthy Hormones supported the listing of testosterone 1% cream and highlighted the gender disparity that should be addressed. RANZCOG highlighted the prohibitive cost of newer medications that do not have PBS subsidy and stated, “more needs to be done to address the affordability and accessibility of medications available to women in Australia”.

6.7 The PBAC noted the comments received from the ACNP referred to the benefits of testosterone 1% cream for treating vasomotor and other symptoms of menopause, which highlighted the perception that testosterone helps improve symptoms of menopause rather than treating HSDD.

Clinical trials

6.8 The claim of superior effectiveness of testosterone 1% cream versus placebo was based on a double-blind, randomised, placebo-controlled, cross-over study (El-Hage, 2007) (each period being of 3 months’ duration) in 36 women who were menopausal (i.e., had follicle stimulating hormone levels >30 U/L), had had a hysterectomy, were not depressed, were in a stable relationship, and who had low sexual function. The enrolled women did not meet diagnostic criteria for HSDD according to the ISSWSH (see paragraphs 4.2 above and 6.16 below) and received a starting dose that was higher (10 mg) than the 5 mg dose recommended in the approved Product Information for AndroFeme 1.

6.9 The claim of superior efficacy of the 5 mg dose versus placebo was based on a pharmacokinetic study (Fooladi, 2015) showing that the 5 mg dose produced serum testosterone levels lower than those observed with the 10 mg dose but within the range recommended by consensus guidelines.

6.10 The claim of non-inferior safety of testosterone 1% cream was based on El-Hage (2007). The submission also referred to "post-market pharmacovigilance data" as evidence of safety and to "years of evidence in real-world application" as evidence of safety and efficacy, but no such data were presented in the submission.

6.11 To counter the fact that the El-Hage (2007) study recruited only surgically postmenopausal women, the submission stated that "Effectiveness and safety of therapy in naturally postmenopausal patient population has been studied (Davis 2017)", but this appears to be the unpublished pharmacokinetic study titled "An open-label, phase 2, single centre, randomised, crossover pharmacokinetic study assessing two application areas of 0.5 ml (5 mg) AndroFeme 1 cream in healthy postmenopausal women" (Table 2-3, pp51-52 of the submission), which enrolled only 16 women (Table 2-4, p53 of the submission). No data from this study were provided in the submission.

6.12 There have been a number of randomised controlled trials of topical testosterone, mostly using patch or gel preparations, for treatment of HSDD in postmenopausal women. These were excluded from the primary analysis because they did not use

testosterone cream. However, the submission sought to rely on the results as demonstrating a class effect of testosterone which it stated could be assumed to apply to 1% testosterone cream, given that the serum testosterone levels in the pharmacokinetic study were broadly similar to those in the trials of patches. These trials were not included individually but through a systematic review and meta-analysis (Islam, 2019).

6.13 Details of the submitted trials and the systematic review are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial or Study ID	Protocol title/ Publication title	Publication citation
El-Hage, 2007	El-Hage G, Eden JA, Manga RZ. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder.	Climacteric 2007; 10:335-43.
Fooladi, 2015	Fooladi E, Reuter SE, Bell RJ, Robinson PJ, Davis SR. Pharmacokinetics of a transdermal testosterone cream in healthy postmenopausal women.	Menopause 2015; 22:44-9.
Islam, 2019	Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data.	Lancet Diabetes Endocrinol 2019; 7:754-766.

Source: Table 2-3, pp51-52 of the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
El-Hage, 2007	36	R but method not ideal; DB; T 10 mg or placebo for 12 weeks, 4 week washout, then cross-over to placebo or T 10 mg for 12 weeks.	Unclear [a]	Menopausal women, recruited by advertisement; hysterectomy ± ovariectomy; BISF-W <33.6; stable relationship; not depressed; distress at low sexual interest not assessed or required; all treated with transdermal estradiol for the duration of the study.	Primary: Domain 1 (Thoughts and desire) score of BISF-W.
Fooladi, 2015	7	R (method not stated), OL; cross-over study, with R to T 5 mg or 10 mg dose first then cross-over to the other; each treatment period was 21 days, no washout.	Not applicable	Healthy, naturally postmenopausal women aged 50-65; no systemic hormones.	Pharmacokinetics
Islam, 2019	8480 women in 46 reports of 36 RCTs; outcomes for sexual function were reported in 15 studies in 3766 postmenopausal women & 3 studies in 226 premenopausal women; 13 trials used transdermal patch, 2 used transdermal gel, one used transdermal spray, 2 used 1% testosterone cream (El-Hage, 2007 and a trial in premenopausal women).				Sexual desire, satisfying sexual events; adverse events.

Source: El-Hage et al. Climacteric 2007; 10:335-343; Fooladi et al. Menopause 2015; 22:44-49; Islam et al. Lancet Diabetes Endocrinol 2019; 7:754-766.

BISF-W = Brief Index of Sexual Functioning for Women; DB = double blind; OL = open label; R = randomised; RCT = randomised controlled trial; T = testosterone.

[a] Randomisation was carried out on site and the person who carried out the randomisation and labelled the active and placebo creams communicated with the research staff.

6.15 El-Hage (2007) was graded as having unclear risk of bias because randomisation was carried out on site and the person who carried out the randomisation and labelled the active and placebo creams communicated with the research staff.

6.16 The ESC noted that it was not an inclusion criterion in El-Hage (2007) that women have significant personal distress related to a low level of sexual interest. They were recruited by advertisements, not from clinics, so they may never have sought care for low sexual interest and personal distress cannot be inferred. For this reason alone, they did not meet the diagnostic criteria for HSDD according to the ISSWSH. Patients were included in the trial if they had, among other things, decreased sexual function based on a total Brief Index of Sexual Functioning for Women (BISF-W) score of less than 33.6; however, 33.6 was the mean score of a convenience sample of 187 healthy women, with partners, aged 20-55 years in New Jersey. The standard deviation of the score in this sample was 12.4, and the range was 0.2 to 63.0, so the evaluation noted that there is no basis on which to define scores below 33.6 as abnormal (Mazer, 2000). Further, the BISF-W asks for responses for the last month, so a single score does not satisfy the diagnostic requirement for HSDD of at least six months loss of sexual interest.

6.17 Women in El-Hage (2007) were menopausal (i.e., had elevated follicle stimulating hormone levels >30 U/L) and were required to be using transdermal estradiol.

Specifically, they were required to have had a hysterectomy but may or may not have had ovariectomy - i.e., they may or may not have been surgically menopausal. Although a post-hoc analysis comparing women who had had ovariectomy with those who had not was reported, the number of women who had had ovariectomy was not provided.

Comparative effectiveness

Results of the randomised controlled trial (El-Hage 2007)

6.18 Efficacy outcomes in El-Hage (2007) are shown in Table 4.

Table 4: Efficacy outcomes in the submitted trial – El-Hage (2007)

Outcome	Testosterone 10 mg daily	Placebo
Baseline BISF-W Domain 1 (Thoughts/desire) Mean (SD)	1.15 (1.29)	1.51 (1.41)
BISF-W Domain 1 (Thoughts/desire) at 12 weeks Mean (SD)	2.55 (1.96)	1.73 (1.95)
Change from Baseline BISF-W Domain 1 (Thoughts/desire) Mean (SD)	1.41 (2.08)	0.18 (2.17)
P value for CFB BISF-W Domain 1 (Thoughts/desire) vs placebo	0.024	
Baseline BISF-W Total Score Mean (SD)	19.85 (10.67)	21.05 (10.41)
BISF-W Total Score at 12 weeks Mean (SD)	28.45 (11.28)	21.52 (12.57)
Change from Baseline BISF-W Total Score Mean (SD)	8.76 (7.46)	0.54 (9.16)
P value for CFB BISF-W Total Score vs placebo	<0.001	
Serum Testosterone, nmol/L[a] Mean (SD) Baseline 12 weeks	 2.1 (1.2) 3.8 (2.5)	 1.6 (0.5) 1.7 (0.4)
Baseline POMS, Total Score Mean (SD)	166.63 (30.45)	171.93 (31.96)
POMS, Total Score at 12 weeks Mean (SD)	177.42 (30.21)	178.62 (33.52)
Baseline DASS Total Score Mean (SD)	8.21 (9.74)	6.64 (7.81)
DASS Total Score at 12 weeks Mean (SD)	4.34 (7.43)	5.77 (9.48)

Source: El-Hage et al. Climacteric 2007; 10:335-343, Table 2 and Table 3.
BISF-W = Brief Index of Sexual Functioning for Women; CFB = change from baseline; DASS = depression-anxiety-stress score - higher scores = greater psychological distress; POMS = profile of mood states - higher scores = greater mood disturbance; SD = standard deviation.
[a] Testosterone nmol/L / 3.467 = ng/mL.

6.19 No minimum clinically important difference (MCID) has been defined for the BISF-W or its domains, so it is not clear whether the changes associated with testosterone treatment were clinically meaningful. However, the normative mean (SD) and median (range) scores for Domain 1 of the BISF-W defined by Mazer (2000) were 5.31 (2.16) and 5.29 (0.29, 11.29), respectively. The increase in the Domain 1 score seen with

testosterone treatment in the trial was less than one standard deviation of the normative Domain 1 score and left most women well below the mean and median normative values.

6.20 There was no beneficial effect of testosterone on mood or energy, as measured by the profile of mood states (POMS) and depression-anxiety-stress score (DASS). Although the DASS declined more in the testosterone treatment period than in the placebo treatment period, the difference was not statistically significant (P = 0.528). The PBAC noted that the difference in the POMS between testosterone and placebo treated patients was not statistically significant (P = 0.763).

6.21 Testosterone levels were measured by radio-immuno assay. This method is considered unreliable in the female range (Davis, Baber, 2019). However, the results were broadly consistent with those reported by Fooladi (2015) using liquid chromatography tandem mass spectroscopy (LC-MS/MS).

6.22 Mean testosterone levels at baseline were below the upper limit of normal (ULN) defined by the study: <2.6 nmol/L = 0.75 ng/mL (this was higher than the ULN for healthy premenopausal women defined by Fooladi (2015): 1.70 nmol/L = 0.49 ng/mL; El-Hage, 2007 does not give the source of its reference value or the population it refers to). Mean testosterone levels during treatment were above the ULN defined by the study, and some women must have had levels several times the ULN. This is not consistent with the proposed restriction or with the international consensus statement, which recommends dosing that approximates levels of testosterone in healthy premenopausal women.

6.23 Fooladi (2015) reported that testosterone 5 mg produced a mean level slightly above the ULN for premenopausal women (0.52 ng/mL vs 0.49 ng/mL), and a median level within the normal range (0.38 ng/mL). However, the range was 0.37-1.10 ng/mL, so some women receiving 5 mg doses had levels twice the ULN. After a 10 mg dose the median level was almost twice the ULN for premenopausal women, consistent with the results from El-Hage (2007).

6.24 The submission stated that the results of Fooladi (2015) "confirm the dose-response relationship without compromising safety". The ESC agreed with the evaluation that this claim was not justified by the data.

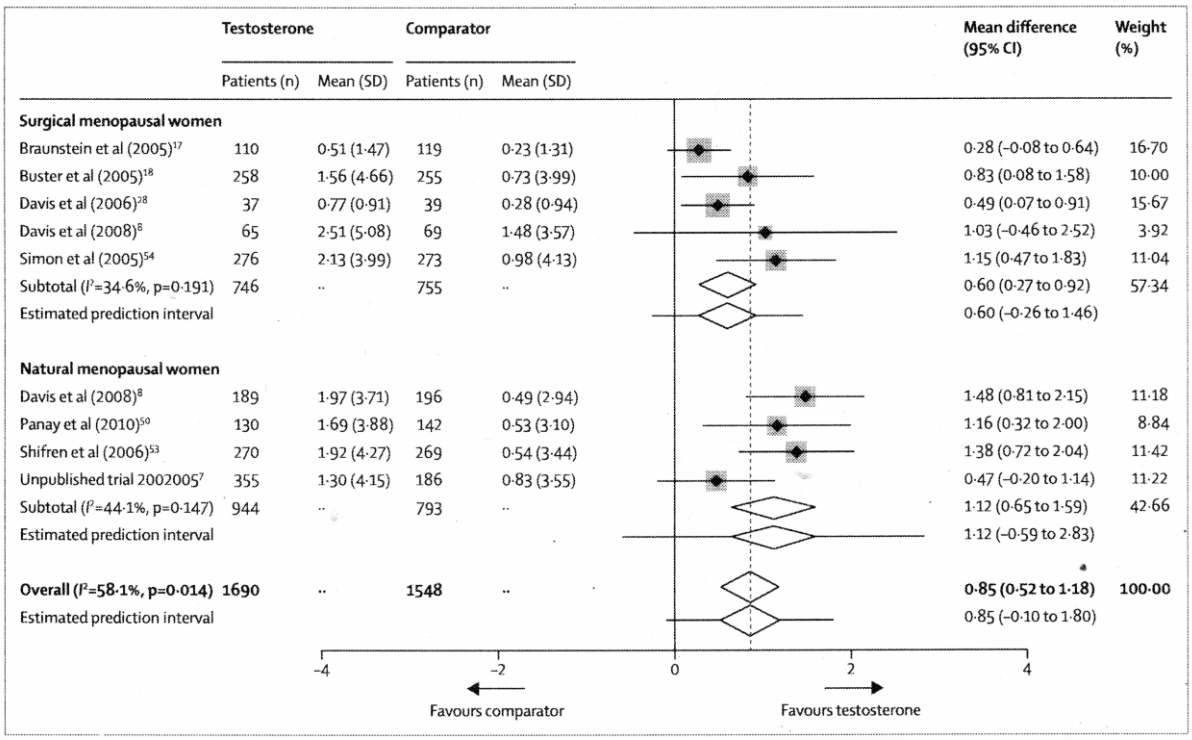
Results of the systematic review and meta-analysis

6.25 The ESC agreed with the evaluation that the results of the systematic review and meta-analysis should be interpreted with caution. Most of the studies included in the systematic review appropriately excluded women with identifiable causes of reduced sexual function, such as a dysfunctional relationship, dyspareunia, depression, or antidepressant use, but did not otherwise use a consistent definition of sexual dysfunction, and many patients in the trials may not have had HSDD by the criteria of the ISSWSH pathway of care. Further, nearly half the included studies were graded as having a high risk of attrition bias. Finally, the results may be compromised by

publication bias, since two large, randomised, placebo-controlled trials of a testosterone gel (Libigel®) that failed to show any benefit to sexual function were excluded because they have been published only in abstract. The ESC additionally noted that most of the trials investigated the use of products other than 1% testosterone cream.

6.26 The Forest plot for the frequency of satisfying sexual events, by menopausal status (surgical or natural), is shown in Figure 1.

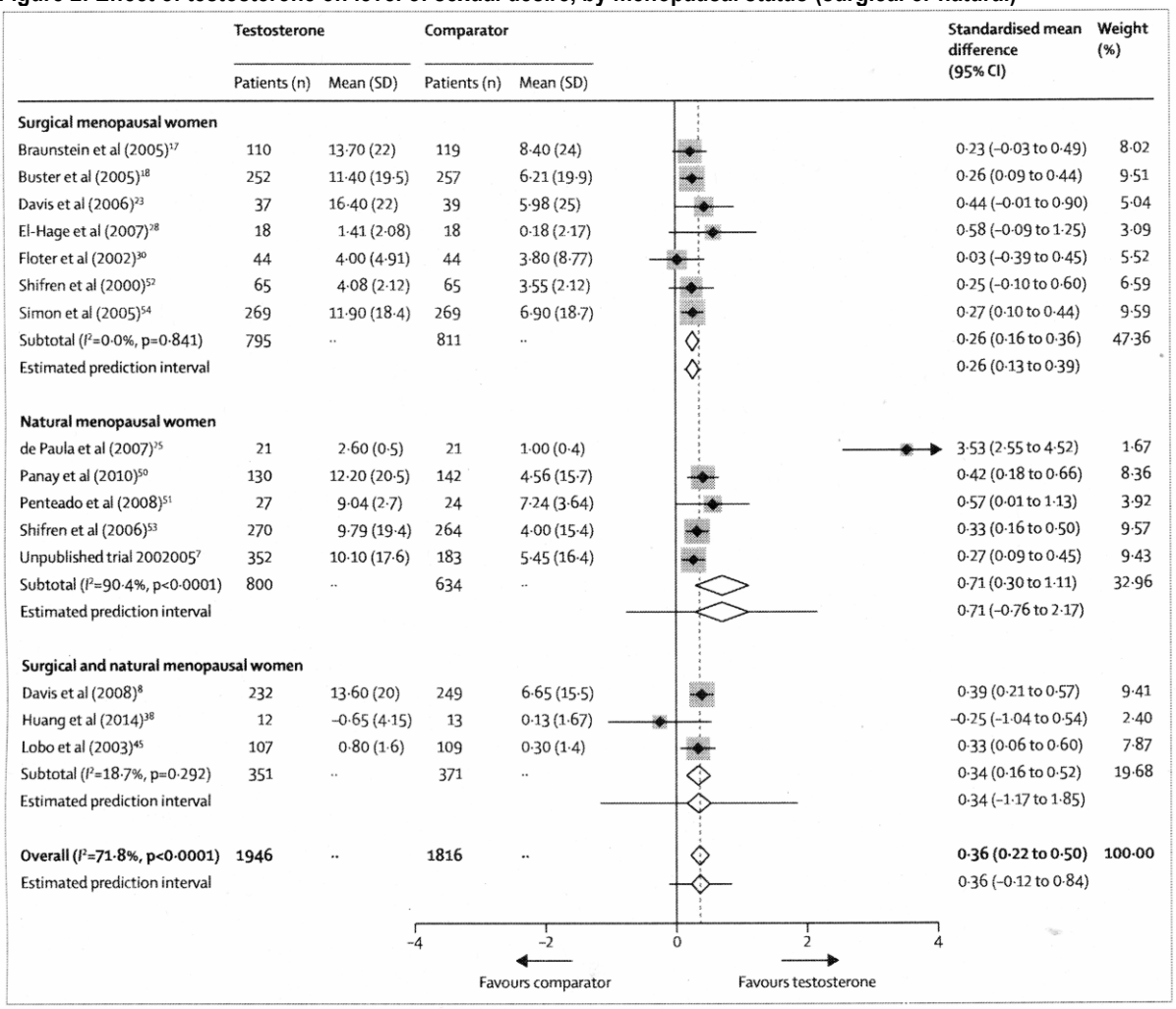
Figure 1: Effect of testosterone versus comparator on satisfying sexual events, by menopausal status (surgical or natural)



Source: Islam R, et al. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol 2019; 7:754-766.

6.27 The Forest plot for effects on sexual desire, by menopausal status (surgical or natural), is shown in Figure 2.

Figure 2: Effect of testosterone on level of sexual desire, by menopausal status (surgical or natural)



Source: Islam R, et al. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol 2019; 7:754-766.

6.28 Although the pooled effect of testosterone on the frequency of satisfying sexual events was statistically significant, it was less than one additional satisfying sexual event per month above a baseline frequency of about three events per month. The ESC noted that no MCID for this outcome has been agreed.

6.29 Because of the relatively high level of heterogeneity among the studies, the 95% confidence intervals for the predicted effects in future studies included zero for both surgically menopausal and naturally menopausal women.

6.30 In 2000, the US Food and Drug Administration issued guidance recommending the frequency of satisfying sexual events as an outcome measure in trials of treatment for

female sexual dysfunction.[8] For this reason, the frequency of satisfying sexual events was widely used as an outcome measure in trials done between 2000 and 2010. However, this is no longer the FDA's recommendation and the international consensus statement on testosterone therapy for women recommended that the frequency of satisfying sexual events should not be a primary efficacy measure in future trials of treatment for female sexual dysfunction (Davis, Baber, 2019). The evaluation considered that this casts doubt on the usefulness of most of the trials in the systematic review.

6.31 Although the pooled effect of testosterone on sexual desire was significant, there is no agreed MCID for this outcome, so the clinical significance of this result could not be assessed. Because of the relatively high level of heterogeneity among the studies, the 95% confidence intervals for the predicted effects in future studies included zero for this outcome for naturally menopausal women.

6.32 The ESC noted that there was no evidence that testosterone improved mood or well-being.

6.33 Serum testosterone levels on treatment in trials reporting them are shown in Table 5. The ULN for serum testosterone in premenopausal women used by Fooladi (2015) was 0.49 ng/mL, and the upper limit of the reference range used by El-Hage (2007) was 0.75 ng/mL (the group for which that reference range pertained to was not stated).

6.34 Mean or median testosterone levels were below the ULN for premenopausal women for the assay used in Shifren (2006) and in women receiving the lower testosterone dose in Shifren (2000). In all other trials, most women had testosterone levels above the ULN.

[8] Pyke RE. FDA decisions on measures of Hypoactive Sexual Desire Disorder in women: A history, with grounds to consider clinical judgment. *Sexual Medicine Reviews* 2021; 9:186–193.

Table 5: Serum testosterone levels in testosterone treated-patients in the trials included in the systematic review and meta-analysis and reporting serum testosterone, and in Fooladi (2015).

Study	Serum testosterone at end-of-treatment, ng/mL
Buster, 2005 N = 252 Median (10th, 90th centiles) [ULN for the assay used, ng/mL]	 0.66 (0.23, 1.46) [0.50]
El-Hage, 2007 N = 36 Mean (SD) [ULN for the assay used, ng/mL]	 1.09 (0.72) [0.75]
Shifren, 2000 N = 65 Mean (SD) Testosterone 150 mcg/day Testosterone 300 mcg/day [ULN for the assay used, ng/mL]	 0.64 (0.25) 1.02 (0.39) [0.68]
Simon, 2005 N = 269 Median (10th, 90th centile) [ULN for the assay used, ng/mL]	 0.70 (0.33, 1.39) [0.50]
Panay, 2010 N = 130 Mean [ULN for the assay used, ng/mL]	 0.68 [0.50]
Shifren, 2006 N = 270 Median (10th, 90th centile) [ULN for the assay used, ng/mL]	 0.54 (0.20, 1.19) [0.73]
	Serum testosterone at 21 days, ng/mL
Fooladi (2015), 5 mg dose Mean (SD) Median (range) [ULN for the assay used, ng/mL]	 0.52 (0.32) 0.38 (0.37, 1.10) [0.49]

Source: Constructed during the evaluation from published reports.
SD = standard deviation; ULN = upper limit of normal.

6.35 The mean and median levels reported by Fooladi (2014) for a 5 mg dose were below the levels reported in the trials included in the systematic review. Based on these results, the beneficial effects of a 5 mg dose of testosterone 1% cream may be smaller than those observed in the trials.

Comparative harms

6.36 No serious adverse events were reported in the submitted trial (El-Hage, 2007). Neither acne nor hirsutism were reported as an adverse event.

6.37 In the systematic review and meta-analysis (Islam, 2019), serious adverse events were not more frequent with testosterone. However, data from 3,264 patients in 11 studies showed that testosterone was associated with a greater likelihood of acne, with a relative risk (95% CI) of 1.46 (1.11, 1.92), and data from 4178 patients in 11 studies showed a greater likelihood of increased hair growth, with a relative risk (95% CI) of 1.69 (1.32, 2.14).

6.38 There were no long-term safety data (i.e. more than 2 years) provided.

Benefits/harms

6.39 The data presented in the submission did not allow for a quantitative comparison of the benefits and harms of testosterone 1% cream and placebo in the PBS eligible population. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.40 The submission described testosterone 1% cream as superior in terms of effectiveness compared to placebo. The evaluation considered that this claim was not adequately supported by the evidence presented, because the only trial presented was small (N=36), used a higher dose (10 mg/day) than proposed (5 mg/day) for initial treatment, and enrolled only menopausal women who had undergone hysterectomy and did not meet the diagnostic criteria for the condition specified in the restriction. The PSCR stated that the TGA considered "the dosage recommendations were made on the basis of the totality of available evidence, i.e. that a 5 mg dose will deliver testosterone in female physiological concentrations in most patients, with 10 mg reserved for patients who remain symptomatic and have not exceeded female physiological levels of testosterone by more than 50% after a 12-week trial". The Pre-PBAC Response stated that the TGA approved testosterone 1% cream for the treatment of HSDD based on "a comprehensive set of clinical data, including supportive bridging data from testosterone patch trials and broader transdermal studies". The Response asserted that "the entirety of this body of evidence must be considered in the evaluation. This includes studies that enrolled women with and without estrogen use and across both surgical and natural menopause, reflecting the same population intended for PBS access".

6.41 The evaluation further noted that, while the pooled effect of testosterone on the frequency of satisfying sexual events was statistically significant, this outcome is no longer recommended as a primary efficacy measure for female sexual dysfunction (Davis, Baber, 2019). Taking all the available evidence into consideration, the evaluation considered it reasonable to conclude that testosterone 1% cream is likely to benefit some women, but the magnitude of the effect was probably overestimated because the proposed dose (5 mg/day) leads to serum testosterone levels lower than those seen in trials with positive results. In relation to the degree and magnitude of benefit, the PSCR highlighted that dispensing records from two Western Australian pharmacies covering 8,924 women showed a typical trial-of-therapy pattern with a substantial long-term cohort. The PSCR stated that from this dataset, "60.8% continued for ≥3 months, 46.2% for ≥6 months, 30.7% for ≥12 months, 18.9% for ≥24 months, 13.8% for ≥36 months, and 7.22% for ≥60 months. 375 women (4.2%) remained on therapy for >7 years, underscoring sustained real-world use among responders".

6.42 The ESC considered that for some women, testosterone 1% cream may be superior to placebo. However, the ESC also considered that the proportion of women who might benefit and the degree of benefit they might attain is highly uncertain based on the clinical evidence presented. The PBAC noted that while some women may benefit from testosterone, it considered on balance that the claim of superior comparative effectiveness was not adequately supported by the data.

6.43 The submission described testosterone 1% cream as non-inferior in terms of safety compared to placebo. The ESC agreed with the evaluation that this claim was not adequately supported. There was a lack of safety data presented, with the submitted trial (El-Hage, 2007) being small and conducted over a short period of time [only 2 years]. While testosterone increases sexual interest over a few weeks, the evaluation and the ESC noted that other (potentially negative) effects may take much longer to appear. The Pre-PBAC Response stated that "Whilst formal clinical trial safety data beyond 2 years is limited, AndroFeme 1 has been prescribed in Australia for over 25 years and the UK since 2017. In that time only three adverse drug reactions have been recorded in the TGA Database of Adverse Event Notifications (skin rash, elevated T level and suspected UTI) and none in the MHRA Yellow Cards database". However, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.44 The submission did not present an economic analysis of testosterone against the proposed comparator of placebo.

6.45 The submission proposed a 'cost minimisation approach' (CMA) for the listing of testosterone 1% cream, comparing the price to an existing PBS listed product, testosterone 5% cream (AndroForte 5). The submission stated that this was based on the lowest cost per day that the government is willing to pay for male testosterone products, which it estimated as between $1.07 (for AndroForte 5) and $2.63 (for Testogel pump pack) per day. As no equi-effective dose was proposed, the ESC agreed with the evaluation that the analysis was in fact a cost comparison. The key components of the approach are shown in Table 6.

Table 6: Key components and assumptions of the cost comparison

Component	Claim or assumption
Therapeutic claim: effectiveness	Effectiveness is assumed to be superior to placebo
Therapeutic claim: safety	Safety is assumed to be non-inferior to placebo.
Evidence base	Direct randomised trials and meta-analyses from Section 2: El-Hage G, Eden JA, Manga RZ. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder. Climacteric. 2007 Aug;10(4):335-43. Fooladi E, Reuter SE, Bell RJ, Robinson PJ, Davis SR. Pharmacokinetics of a transdermal testosterone cream in healthy postmenopausal women. Menopause. 2015 Jan;22(1):44-9. Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol. 2019 Oct;7(10):754-766.
Equi-effective doses	Not calculated. Price calculated as the daily cost per day for male testosterone supplementation.
Direct medicine costs	AndroForte 5 50 mL tube DPMQ = $107.87 Testogel 2x60 pump actuations DPMQ = $79.29 Testavan 56 pump actuations DPMQ = $84.74 AndroFeme 1 50 mL tube DPMQ = $107.87
Other costs or cost offsets	Not included

Source: Table 3.1, pp96-7 of the submission.

6.46 The submission did not present any evidence to support the view that the 'value' of the outcomes of testosterone therapy in postmenopausal women would be the same as that for the outcomes for men with androgen deficiency who would qualify for one of the currently PBS-listed testosterone products. The ESC noted that the submission did not provide justification that the price of testosterone products for male hypogonadism could be used as a benchmark for the price of testosterone in women with HSDD. The ESC considered that the value of using testosterone in those two populations may be completely different; therefore, the economic analysis presented by the submission (price per day of treatment), was not an appropriate method to determine cost-effectiveness for HSDD.

6.47 The submission proposed a price on the basis of a comparison with the existing price for the testosterone 5% cream, 50 mg/mL, 50 mL. The ESC considered this was not appropriate. The PBAC last considered this product in March 2021, when the sponsor (also Lawley Pharmaceuticals) applied for an increase in the Approved Ex-Manufacturer Price (AEMP) compared to other topical testosterone products. The basis for the requested increase in price was a reduction in daily dose due to a change in application site (from torso to scrotum) so that the 50 mL tube would provide up to 100 treatments.

6.48 A comparison of AndroFeme 1 with the existing topical testosterone products for male hypogonadism, including the recommended dose based on Product Information documents, price per day based on dose, and price per mg, is shown in Table 7. The

submission indicated that based on the comparison of daily drug cost based on DPMQ, the least expensive of the available currently listed testosterone products is AndroForte 5, which like AndroFeme 1, has a 50 mL pack size and a recommended daily dose of 0.5 mL. The submission stated that price parity between the 2 products would result in a DPMQ for AndroFeme 1 at the same price as AndroForte 5 (currently $107.87 for 1 pack). However, the submission assumed a maximum number of days coverage based on the minimum recommended daily doses in order to calculate a daily drug cost; instead, the evaluation considered that the comparison should reflect a price per mg based on pack size and AEMP.

6.49 Based on the comparison of price per mg based on pack size, the evaluation calculated that the sponsor requested a price per mg of testosterone that was up to five times higher for HSDD in postmenopausal women compared to existing testosterone products that may potentially be being used for HSDD. The PSCR asserted that, "mg-for-mg pricing is not a valid or safe basis for evaluating transdermal testosterone". The PSCR highlighted that "systemic exposure from skin delivery depends on formulation pharmacokinetics and site of application, not just nominal milligrams" and stated that "testosterone creams/gels demonstrate non-linear absorption; therefore, "mg" does not translate proportionally to effect or cost-effectiveness".

6.50 The ESC was of the view that a "mg per mg" price comparison was a more reasonable approach to determining cost-effectiveness than the approach used by the submission (price per day of treatment), noting that while the submission argued that this comparison was not appropriate given the different formulations, it contradicted this argument by relying on data from trials that had used different topical testosterone preparations to support there being "a class effect of testosterone which can be assumed to apply to 1% testosterone cream given similar serum testosterone levels were demonstrated in a pharmacokinetic study". The ESC further noted that the excipients used in the formulation of 1% testosterone cream were the same as those used in the formulation of AndroForte 5.

6.51 The evaluation noted that the comparison presented did not include the cost of non-oral estrogen therapy. The PSCR stated that "Evidence underlying the registration and dosing shows AndroFeme 1 achieves physiologic female testosterone levels without systemic estrogen" and that "the use of estrogen therapy is standard for postmenopausal women requiring hormone replacement therapy and is not specific to the treatment of HSDD".

6.52 The comparison presented did not include the cost of monitoring of testosterone levels. The Product Information (PI) states that baseline testosterone and sex hormone binding globulin (SHBG) levels should be obtained and that the test should be repeated at 3 to 6 weeks following therapy. The PI additionally states that the serum concentration of total testosterone should be maintained within the approximate physiological range for premenopausal women. The ESC considered that the cost of measuring testosterone levels at: baseline, 3-6 weeks after initiating

treatment, at 12 weeks ("full assessment") and then 6-monthly, should be included in the economic evaluation.

6.53 The ESC noted that the economic analysis had not captured the cost of diagnosis and assessment of women for HSDD. The PSCR stated that, "sexual assessment is now a standard, funded part of menopause management in Australia: from 1 July 2025, new MBS menopause/perimenopause health-assessment items commenced … to support comprehensive clinical assessment (including sexual function), meaning these professional time costs are already covered and not specific to AndroFeme 1". The ESC considered that HSDD is explicitly not a condition of menopause and that the economic evaluation should include the cost of assessment.

6.54 The submission stated that women using currently listed testosterone products are at greater risk of adverse events than men but argued that the 1% cream product would have fewer adverse events and would therefore be more cost-effective. No evidence to support this claim was provided. As described in paragraphs 6.37 and 6.43, adverse events observed in clinical trials of testosterone patches and gels in women with HSDD suggest that troublesome acne and hirsutism are likely to occur with use of 1% testosterone cream.

6.55 The submission stated that the price requested would provide price parity and gender equity compared to existing products.

Table 7: Comparison of prices of PBS listed topical testosterone products

Product	Concentration	Total amount testosterone per pack	Recommended daily dose	Number of days/pack (max-min)	DPMQ	Price/day based on dose	Price/mg based on pack size	AEMP	AEMP/day based on dose	AEMP/mg based on pack size
AndroForte 5	50 mg/mL	50 mL = 2500 mg	25-100 mg	100-25	$107.87	$1.07–$4.28	$0.043	$87.50	$0.875 - $3.50	$0.035
Testogel 1%	12.5 mg per actuation	2 x 60 x 12.5 = 1500 mg	50 mg/day = 4 actuations to 100 mg/day = 8 actuations	30-15	$79.29	$2.63-$5.28	$0.053	$60.92	$2.03 - $4.06	$0.041
Testogel	50 mg/5 g gel	30 x 5 g sachets = 1500 mg	50 mg/day = 1 sachet to 100 mg/day =2 sachets	30-15	$79.29	$2.63-$5.28	$0.053	$60.92	$2.03 - $4.06	$0.041
Testavan 2%	23 mg per actuation	56 actuations = 1288 mg	1-2 actuations/day	56-28	$84.74	$1.51-$3.13	$0.066	$65.99	$1.18 - $2.36	$0.051
AndroFeme 1	10 mg/mL	50 mL = 500 mg	5-10 mg/day	100-50	$107.87	$1.07-$2.16	$0.216	$87.50	$0.875-$1.75	$0.175

Source: Compiled during the evaluation.
AEMP = approved ex-manufacturer price; DPMP = dispensed price for maximum quantity.

Drug cost/patient/year

6.56 Based on the proposed price, if used at a dose of 5 mg per day, the cost per patient per year would be $383.72 (3.65 packs per year *$107.87 per pack).

Estimated PBS usage & financial implications

6.57 The submission used a market share approach to estimate the utilisation and cost of listing testosterone 1% cream on the PBS. The source of the market estimate was the current private prescription market for the product, derived from the sponsor's sales data. The key inputs are shown in Table 8.

Table 8: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Drug prices, quantities, item codes, indication, clinical setting	PBS online. Accessed Jan 2024 [ibid]	
PBS/RPBS utilisation data	PBS and RPBS utilisation statistics. Accessed from http://medicarestatistics.humanservices.gov.au/ in January 2024. To calculate patient beneficiary category distribution for 1% testosterone cream in the first year of PBS listing, using estradiol as the closest proxy for benefit categories. 98.73% PBS scripts and 1.27% RPBS.	May be reasonable.
Private market 1% testosterone cream scripts	See 'Attachment 4_AF1_Budget Impact Model – AndroFeme 1 BIM (Worksheet '2e. Scripts – market')'. Dispensed unit trends for 1% testosterone cream in previous years to provide estimates for uptake of market share.	Stated to be sales data but could not be independently verified. States that the last full year – 2024 – supply was 47,376 scripts. Note supply prior to TGA registration.
Growth rate	10% per year, sponsor assumption.	Could not be independently verified. Likely an underestimate. Sales data provided by the sponsor showed growth was 94% from 2022 to 2023 and 86% from 2023 to 2024.
Market share	[redacted]%, assumes all patients currently treated will transition to PBS supply.	Sponsor assumption could not be independently verified. Does not account for patients using currently PBS-listed testosterone products, private scripts off-label of other existing testosterone products, or for patients who have testosterone compounded.
Dose /duration	1 tube of cream expected to last 100 days; assumes 3.65 tubes per year.	Assumes no increase in dose. This is unlikely to be correct. Not clear how long therapy is assumed to continue; may be ongoing.

Source: Compiled from Table 4.1, p102 of the submission and associated text Section 4; Financial Workbook Sheet 2e.

6.58 The submission did not allow for any increase in the market for testosterone 1% cream, assuming that all patients who require it would be accessing it as a private script or off-label with a PBS prescription for one of the 4 PBS-listed products. An increase in use of 1% testosterone cream is likely with a PBS listing. A combined epidemiological/market-share approach would have been more appropriate to estimate the financial impact of listing 1% testosterone cream on the PBS.

6.59 The estimated use and cost as presented in the submission is shown in Table 9. The submission assumed year 1 was 2025 and based the estimate of scripts on a 10% annual increase from 2024.

Table 9: Estimated use and financial implications

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Estimated extent of use						
Number of scripts dispensed[a]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][4]
Estimated financial implications of testosterone 1% cream						
Cost to PBS/RPBS less copayments	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Estimated financial implications for other medicine						
Cost to PBS/RPBS less copayments	0	0	0	0	0	0
Net financial implications						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net increase to Services Australia [b]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][4]

Source: Tables 4.2, p105; Table 4.4 and Table 4.5 p106 of the submission

[a] Assuming 3.65 scripts per year as estimated by the submission.

[b] The Financial Workbook Sheet 3a as referenced in Table 4.4 has very slightly different numbers of scripts.

The redacted values correspond to the following ranges:

[1] *50,000 to < 60,000*

[2] *60,000 to < 70,000*

[3] *70,000 to < 80,000*

[4] *80,000 to < 90,000*

[5] *$0 to < $10 million*

6.60 There appeared to be an inconsistency between the submission Main Body and the Financial workbook estimate of the impact on prescription processing by Services Australia. The submission appeared to assume that the listing would be as a Restricted Benefit whereas the Workbook used an Authority Required listing. The latter would be consistent with the existing listings for topical testosterone.

6.61 The total cost to the PBS/RPBS of listing testosterone 1% cream was estimated to be $0 to < $10 million in Year 6, and a total of $40 million to < $50 million in the first 6 years of listing. No sensitivity analyses were presented in the submission.

6.62 In the absence of validated private market data, and given the likely underestimate of market expansion, these estimates could not be verified by the evaluation. However, if the product were to be made available through a Restricted Benefit and with access possible through nurse prescribers, it is highly likely that the estimates would be a significant underestimate. In addition, the estimates did not include potential costs to the MBS of monitoring testosterone concentration and SHBG as recommended in the PI.

6.63 DUSC considered the estimates presented in the submission to be extremely uncertain and due to the use of non-medical eligibility criteria, impossible to determine. DUSC identified the main issues as:

- The submission requested a Restricted Benefit listing without a clear restriction or stopping rules.
- The condition is not medically definable and relies on psychosocial factors such as "distress", which is highly subjective.
- The screening test has a high risk of bias as it appears to be based on commitment questions directing respondents to a desired outcome. DUSC considered that it was not an objective screening tool and involved persuasive communication techniques.
- The clinical trial did not match the PBS population.
- There is high likelihood for use outside of the restriction.
- The epidemiology of the condition is poorly understood.
- There was no reliable way to estimate the number of patients who might use testosterone for HSDD.

6.64 Overall, DUSC considered the utilisation and financial estimates presented in the submission could not be verified due to the restricted benefit and non-medically psychosocial factor of "distress" as a measurement being subjective and extremely vulnerable to the method of screening and marketing. DUSC further considered that there is a likelihood of increased diagnosis and use over time, including increased utilisation within and beyond the indication.

Quality Use of Medicines

6.65 The submission did not provide any information about quality use of medicines.

6.66 The sponsor commented in the PSCR on the proposed approach to avoid inadvertent exposure or use of testosterone 1% cream in women of reproductive age:

- "All educational and marketing material provided by the Sponsor to clinicians strictly adheres to the TGA indication and Product Information, which is for use in postmenopausal women. Additionally, the Sponsor collaborates regularly with the Australasian Menopause Society for clinical education purposes, to ensure clinicians are aware of the appropriate indications and precautions for use, in alignment with local and international treatment guidelines and regulations".
- The Sponsor also emphasised that "the Product Information outlines the notable risks associated with testosterone use in women of reproductive age. This significant risk means that women in this age group are unlikely to use testosterone when informed by their medical practitioner of these precautions".
- The Sponsor stated that they are "committed to collaborating with the PBAC and the Department going forward to ensure quality use of medicines and avoid exposure to testosterone in inappropriate populations".

- The Sponsor stated that they are "particularly concerned about the population of women that are using male testosterone formulations against TGA precautions and treatment guidelines, which conflicts significantly with the quality use of medicines".

6.67 DUSC identified the following quality use of medicines risks:

- Risks of promoting a perceived sick state in otherwise healthy women.
- Risk of overexposure and side effects.
- Side effects for long term use not being adequately known.
- Concerns regarding telehealth and promotional activities influencing consumer use, including use outside of the restriction.
- Adverse effects could include polycythaemia causing stroke.
- Application of doses above recommended can produce androgenisation.

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

7 PBAC Outcome

7.1 The PBAC did not recommend testosterone 1% cream for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women. The PBAC questioned the clinical place of testosterone in therapy, noting the difficulty in defining the medical condition and an appropriate scope of testosterone use. The PBAC considered the strength of the comparative clinical evidence presented to be low and noted that inappropriate use of testosterone is associated with adverse effects. The PBAC considered that there would be a high risk of use outside the restriction, and that the proposed price was not supported.

7.2 The PBAC considered the primary reason for this outcome was due to the clinical evidence provided in the submission from the pivotal trial and the meta-analysis.

7.3 The PBAC questioned the clinical place in therapy for testosterone 1% cream. The PBAC acknowledge the high number of comments from consumers, health care professionals and organisations, with many comments supporting the requested listing. However, the PBAC noted that the comments described a range of benefits that did not describe the requested restriction of HSDD, indicating a perception that testosterone will have other benefits that have not been evaluated. The Committee further noted that the comments indicated there was use outside the approved TGA indication (for brain fog, memory or mood issues, dementia, energy, muscle strength, bone strength, hot flushes), in patients who were not postmenopausal, and that some health care professionals and organisations did not support listing of testosterone 1% cream on the PBS. The PBAC specifically noted that many of the inputs suggested that consumers and health care professionals inappropriately equated HSDD with low libido, having used the terms synonymously.

7.4 While the PBAC considered that placebo was the appropriate main comparator, it acknowledged that PBS-listed topical testosterone preparations, private prescription of other testosterone preparations, or compound testosterone preparations, may also be relevant comparators because they are being used and would be hypothetically replaced.

7.5 The PBAC noted that the submission presented the results of the El-Hage (2007) trial in support of its clinical claim of superiority versus placebo. While the PBAC noted that the El-Hage (2007) showed there was a statistically significant increase in the Brief Index of Sexual Function for Women (BISF-W) total score and the BISF-W thoughts/desire domain for patients treated with testosterone 1% cream (10 mg per day) compared to placebo after 12 weeks, the PBAC additionally noted that this trial did not specifically recruit patients that were representative of those for whom PBS-listing was requested (patients were not required to have clinically significant personal distress related to a low level of sexual interest, as is required to meet the definition of HSDD according to the ISSWSH criteria, nor were they required to have failed to respond to appropriate education and correction of modifiable biopsychosocial factors, as is required to meet the proposed PBS clinical criteria). As such, the PBAC considered that the evidence from the trial did not support the clinical claim of superior comparative effectiveness over placebo for the requested patient population.

7.6 While the PBAC noted that the submission had additionally presented a systematic review and meta-analysis published by Islam 2019 to support the clinical claim, the Committee noted that the trials that formed the evidence base for the review and meta-analysis had used an inconsistent definition of sexual dysfunction. The PBAC noted that many patients in the trials may not have had HSDD by the criteria of the ISSWSH pathway of care.

7.7 The PBAC considered that there is potential for androgenisation if testosterone levels are not carefully monitored. The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

7.8 The PBAC noted that the submission had not presented an economic analysis against the nominated comparator of placebo but had requested that the price per day of treatment be the same as for existing PBS-listed testosterone products for males. While the submission argued that it was reasonable that the cost per day of treatment in females should equal the cost per day of treatment in males, the Committee noted that the outcome or benefit for which treatment with testosterone was expected to provide in females versus males was not comparable. The PBAC noted that the submission had not attempted to place a value on the benefit of the improvement in the BISF-W thoughts/desire domain or the BISF-W total score over 12 weeks, and that it was not clear whether the improvements were clinically meaningful as a minimum clinically important difference had not been defined. The PBAC further noted that the cost of treating adverse events associated with using testosterone and the cost of monitoring would be important for an economic analysis versus placebo.

7.9 The PBAC considered the financial estimates were underestimated and that there would be a high risk of use outside the restriction. The PBAC agreed with the DUSC that that the condition relies on psychosocial factors such as "distress", which is highly subjective. Further, the screening test has a high risk of bias as it appears to be based on questions directing respondents to a desired outcome and involved persuasive communication techniques.

7.10 The PBAC considered there was insufficient evidence to support a resubmission.

7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

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 disagrees with the aspects of the factual basis, logic and rationale underpinning the PBAC's decision to not recommend PBS listing of AndroFeme 1.