5.15 TESTOSTERONE
2% w/w enhanced permeation (EP) gel, Testavan®, Ferring Pharmaceuticals Pty Ltd

1 Purpose of Application

1.1 The submission requested an Authority Required (telephone) listing for testosterone 2% enhanced permeation (EP) gel for the treatment of androgen deficiency. This was the first submission to PBAC for testosterone 2% EP gel.

1.2 The requested listing was based on a cost-minimisation analysis of testosterone 2% EP to testosterone 1% gel. The key components of the clinical issue addressed by the submission are summarised below.

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

Component	Description
Population	Patients with androgen deficiency.
Intervention	Testosterone 2% EP gel (TESTAVAN®) applied once daily to clean, dry, intact skin of the shoulder/upper arm.**
Comparator	Testosterone 1% gel (Testogel®) applied once daily to clean, dry, intact skin of the shoulder, upper arm or abdomen.**
Outcomes	Proportion of patients who attain total testosterone $C_{avg(0-24)}$ levels within the normal physiological testosterone levels (10.4-36.4 nmol/L)* (i.e. response rate). The definition of normal physiological testosterone levels, and the timing of the analysis differed between the two studies used in the naïve indirect comparison presented in the submission. Further, no evidence was presented to confirm that 'average levels' are a surrogate for clinical outcomes. For some therapeutics the duration of time above a minimum threshold concentration is relevant to clinical outcomes.
Clinical claim	For patients with androgen deficiency, testosterone 2% EP gel is non-inferior to testosterone 1% gel in bringing serum testosterone into the eugonadal range.

Abbreviations: $C_{avg(0-24)}$ = average concentration over 24 hours; EP = enhanced permeation.
* Testosterone normal physiological range as quoted in the testosterone 2% EP gel (TESTAVAN®) Product Information.
** Throughout this document, when doses are cited they refer to the dose of testosterone (in nmol/L), rather than the dose of gel.
Source: Table 1.1-1, p8 of the submission.

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
TESTAVAN® testosterone 2% EP gel[a]	1	1	5	$[redacted]	Ferring Pharmaceuticals Pty Ltd

[a] 23 mg testosterone per pump actuation, 56 actuations per pack (1,288 mg testosterone /pump pack)
[b] In the financial estimates, a dispensed price for maximum quantity of $[redacted] was used.

Restriction 1 - Established pituitary or testicular disorder	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives

Condition:	Androgen deficiency
Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have an established pituitary or testicular disorder
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 2 - Androgen deficiency is demonstrated through hormone levels	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Androgen deficiency
Treatment criteria:	Must be treated by a specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must not have an established pituitary or testicular disorder AND The condition must not be due to age, obesity, cardiovascular diseases, infertility or drugs
Population criteria:	Patient must be aged 40 years or older
Prescriber Instructions	Androgen deficiency is defined as: i) testosterone level of less than 6 nmol per litre; OR ii) testosterone level between 6 and 15 nmol per litre with high luteinising hormone (LH) (greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14 IU per litre, whichever is higher) Androgen deficiency must be confirmed by at least two morning blood samples taken on different mornings. The dates and levels of the qualifying testosterone and LH measurements must be, or must have been provided in the authority application when treatment with this drug is or was initiated
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 3a – Micropenis	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Micropenis

Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Population criteria:	Patient must be under 18 years of age
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 3b - Pubertal induction	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Pubertal induction
Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Population criteria:	Patient must be under 18 years of age
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 3c - Constitutional delay of growth or puberty	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Constitutional delay of growth or puberty
Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Population criteria:	Patient must be under 18 years of age

Administrative Advice	The name of the specialist must be included in the authority application

2.1 The requested restrictions were identical to those for alternative topical, transdermal testosterone formulations currently listed on the PBS for these indications.

2.2 Three formulations (gel, patch cream) of topical testosterone are already PBS-listed. Testosterone in capsule and injectable forms is also PBS-listed for the conditions described in the requested listing. The ESC considered that the 2% EP gel would be useful and likely easier to use than existing testosterone products due to the shorter time to absorption.

2.3 The requested restrictions differed from the registered TGA indication for testosterone 2% EP gel, which is only for adult male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests:

- The TGA-approved PI states that use of testosterone 2% EP gel is not indicated in children and has not been clinically evaluated in males under 18 years of age. The Pre-Sub-Committee Response (PSCR) stated that the proposed PBS listings were the same as those for currently listed testosterone replacement therapies (TRTs), and noted that other TRTs have been listed on the basis of clinical trials enrolling adult patients. It was further noted that a minority of the total use of TRTs is expected in patients under the age of 18 years of age. The ESC agreed with the PSCR however, noted that this product may be preferred in paediatric populations due to ease of use.
- Neither of the two key clinical studies presented in the submission appeared to have required patients to have clinical features of androgen deficiency at baseline.

2.4 The study population of the key testosterone 2% EP gel study (Study 127) differed from the proposed PBS population:

- None of the patients in the study were under the age of 18 years (relevant to Restrictions 3a-3c);
- Eligibility for the study was based on serum testosterone levels, with no requirement for a clinical diagnosis. The underlying causes of androgen deficiency were not reported in the Clinical Study Report (CSR) for Study 127, and the definition used by the submission to classify patients in Study 127 as having secondary hypogonadism[1] (96% of patients) was not clear.

[1] Secondary hypogonadism is usually defined as hypogonadism caused by a hypothalamic or pituitary disorder. Table 14.1.4.3 of the CSR reported that only 2 (1.3%) of patients had a medical history of hypogonadism as an endocrine disorder, and one patient was reported as having a benign pituitary tumour (Table 14.1.4.3, p174-188 of the CSR).

- Only 4% of patients had an established testicular disorder, while the proportion with an established pituitary disorder was not reported (relevant to Restriction 1);
- Patients were included in the study on the basis of two screening testosterone levels ≤ 10.4 nmol/L, with no requirement to have high luteinising hormone (LH), and patients whose androgen deficiency was due to age or obesity were not excluded from the study. Therefore, the proportion of adult patients in the study who, in the absence of established testicular or pituitary disorders, would have been eligible for treatment under proposed Restriction 2 was uncertain.

3 Background

Registration status

3.1 Testosterone 2% EP gel was approved for registration by the TGA on 26 May 2017 for the following indication: use as testosterone replacement therapy (TRT) for adult male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Previous PBAC consideration

3.2 There has been no previous PBAC consideration for testosterone 2% EP gel.

4 Population and disease

4.1 Androgen deficiency is characterised by deficient testicular production of testosterone[2]. Presenting clinical features of androgen deficiency include non-specific symptoms (lethargy, fatigue, decreased energy and/or endurance, depression, irritability, poor concentration, impaired short term memory, sleepiness, deteriorating work performance, hot flushes), organ-specific symptoms (osteopenia, osteoporosis, reduced muscle mass and strength, increased fat mass and gynaecomastia) and sexual and reproductive symptoms (decreased libido and erectile

[2] Chan I. Assessment and management of male androgen disorders: an update. Aust Fam Physician. 2014; 43 (5):277-82.
Sikaris K, McLachlan RI, et al. Reproductive hormone reference intervals for healthy fertile young men: evaluation of automated platform assays. J Clin Endocrinol Metab. 2005; 90 (11):5928-36.
Yeap BB, Alfonso H, et al. Reference Ranges and Determinants of Testosterone, Dihydrotestosterone, and Estradiol Levels Measured using Liquid Chromatography-Tandem Mass Spectrometry in a Population-Based Cohort of Older Men. The Journal of Clinical Endocrinology & Metabolism. 2012; 97 (11):4030-9

dysfunction)[3]. Australian literature reported that classical androgen deficiency occurs in about 1 in 200 adult men[4,5].

4.2 There is no general agreement on the normal range of serum testosterone, with considerable variation in the reference ranges cited in the Australian literature[6]. In July 2014, the PBAC amended the serum testosterone threshold in the PBS restrictions for testosterone products for men aged 40 years or older who did not have established pituitary disorders to less than 6 nmol/L, or between 6 and 15 nmol/L in combination with high LH (Paragraph 6.1, Testosterone Public Summary Document (PSD), July 2014 PBAC Meeting). Additionally, PBAC recommended that, based on the high degree of variability observed in the measurement of testosterone levels depending on the assay methodology used, serum testosterone assays should be used in combination with a high LH concentration to diagnose androgen deficiency (Paragraph 3.8, Testosterone PSD, August 2013 PBAC Meeting).

4.3 There are currently three topical transdermal formulations listed on the PBS for the same population: cream, patch and 1% gel. When testosterone 5% cream, AndroForte 5® was submitted for PBS consideration, ESC noted that there may not be a compelling clinical need for another topical testosterone preparation. (Paragraph 6.17, Testosterone; 50mg/mL cream, 50 mL; AndroForte 5® PSD, March 2015).

5 Comparator

5.1 The submission nominated testosterone 1% gel, as the main comparator. This was appropriate.

5.2 As outlined above, there are a number of testosterone products currently listed on the PBS. Based on the PBS Therapeutic Relativity Sheets:

- Testosterone transdermal patch was recommended on a cost minimisation basis compared with testosterone undecanoate capsule.
- Testogel®, testosterone transdermal gel 50 mg per 5 g sachet, was listed on a cost minimisation basis versus testosterone transdermal patch releasing 5 mg per day.

[3] Yeap BB, Grossmann M, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust. 2016; 205 (4):173-8.
[4] Conway AJ, Handelsman DJ, et al. Use, misuse and abuse of androgens. Med J Aust. 2000; 172 (5):220-4.
[5] Handelsman DJ, Zajac JD. Androgen deficiency and replacement therapy in men. Med J Aust. 2004; 180:529-35.
[6] Note 2 above

- Axiron®, testosterone transdermal solution was recommended on a cost-minimisation basis compared with testosterone gel. The equi-effective doses are 70 mg testosterone solution and 50 mg testosterone gel.
- Testosterone 1% gel pump bottle was recommended for listing for the treatment of androgen deficiency on a cost minimisation basis with Testosterone 1% gel sachet. The equi-effective doses are testosterone 1% gel 5 g pump bottle and testosterone 1% gel 5 g gel sachet.
- Testosterone 5% cream was recommended for listing for the treatment of androgen deficiency on a cost minimisation basis with the currently listed testosterone 1% gel. The equi effective doses are testosterone 5% cream 100 mg daily and testosterone 1% gel 50 mg daily.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission presented a naïve indirect comparison based on the following studies (note that when doses are cited they refer to the dose of testosterone rather than the dose of gel):

- Study 127 (N = 159) was a Phase 3, open-label, single arm study evaluating the efficacy and safety of testosterone 2% EP gel, in adult men with androgen deficiency, diagnosed on the basis of two fasting morning testosterone levels <10.4 nmol/L, taken at least 3 days apart. The primary efficacy analysis was performed at day 90 from initiation of therapy.
- Swerdloff 2000 (N = 227) was a three arm randomised trial in hypogonadal men with a single morning screening serum testosterone level of ≤ 10.4 nmol/L. Patients were randomised to receive one of two doses of testosterone 1% gel (50 mg testosterone/day or 100 mg testosterone/day), or a testosterone patch (5.0 mg testosterone/day) for 90 days, during which time the study was double-blind with respect to the gels. At 90 days, a single adjustment of the dose of testosterone 1% gel was allowed and patients could continue in an open-label phase, with final efficacy assessments performed on day 180.

6.4 It was not clear how many of the patients enrolled in Study 127 would have been eligible for PBS-subsidised treatment. In Swerdloff 2000, approximately 60% of the patients randomised to testosterone 1% had well defined primary or secondary

hypogonadism, and would have been eligible for PBS-subsidised testosterone under Restriction 1. Thirteen percent of patients had age-related androgen deficiency, while the proportion of the remaining subjects (classified as normogonadotropic hypogonadism) who would have met the criteria in Restriction 2 was uncertain.

6.5 The submission also presented one small (N=11) Phase 1, head-to-head randomised open-label cross-over pharmacokinetic study (CS02) of three testosterone preparations; testosterone 1% EP gel, testosterone 2% EP gel and testosterone 1% gel in down-regulated healthy men. CS02 enrolled healthy adult men with suppressed endogenous testosterone production to mimic hypogonadism. Therefore, the patient group was not representative of any of the 5 groups in the requested listing.

6.6 Details of the studies presented in the submission are provided in the table below.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Testosterone 2% EP gel		
Study 127	Clinical Study Report. A Phase 3, Open-Label, Non-Randomised, Clinical Trial to Evaluate the Efficacy and Safety of FE 999303 (Testosterone Gel) in Adult Hypogonadal Males.	November 2015
	Cunningham G, Belkoff L et al. Efficacy and Safety of a New Topical Testosterone Replacement Gel Therapy for the Treatment of Male Hypogonadism.	*Endocr Pract* 2017; 23:557-565
Testosterone 1% gel		
Swerdloff 2000	Swerdloff R, Wang C et al. Long-Term Pharmacokinetics of Transdermal Testosterone Gel in Hypogonadal Men.	*J Clin Endocrinol Metab* 2000; 85:4500-4510
	Wang C, Swerdloff R et al. Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men.	*J Clin Endocrinol Metab* 2000; 85:2839-2853
	Wang C, Swerdloff R et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men.	*Clin Endocrinol* 2001; 54:739-750
	Wang C, Cunningham G et al. Long-Term Testosterone Gel (AndroGel) Treatment Maintains Beneficial Effects on Sexual Function and Mood, Lean and Fat Mass, and Bone Mineral Density in Hypogonadal Men.	*J Clin Endocrinol Metab* 2004; 89:2085-2098
Head to head pharmacokinetic study		
Study CS02	Clinical Trial Report. A Randomised, Open-Label, Active Control, Multiple Dose, 3-Way Cross-over, Relative Bioavailability Study for two Testosterone Gel (FE 999303) Formulations in Comparison to TESTOGEL in Down-regulated Healthy Men.	June 2011
	Olsson H, Sandström R et al. Pharmacokinetics and Bioavailability of a New Testosterone Gel Formulation in Comparison to Testogel® in Healthy Men.	*Clin Pharmacology in Drug Development* 2014; 3(5):358-364

Abbreviations: EP = enhanced permeation
Source: Table 2.2-2, p29 of the submission.

6.7 The key features of the studies included in the naïve indirect comparison are summarised in the table below.

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

Trial	N	Design/ duration	Risk of bias**	Patient population	Outcomes
Testosterone 2% EP gel (single arm)					
Study 127	160^	Single arm 90 days	High	Adult male with androgen deficiency	The proportion of patients with testosterone $C_{avg(0-24)}$ levels within 10.4 – 36.4 nmol/L at day 90.
Testosterone 1% gel 50mg/day vs. 100mg/day					
Swedloff 2000	151*	OL† 180 days	High	As above	The proportion of patients with testosterone $C_{avg(0-24)}$ levels within 10.4 – 34.7 nmol/L at day 180.

Abbreviations: $C_{avg(0-24)}$ = average concentration over 24 hours; OL=open label; R=randomised.
^ one patient did not receive the treatment and excluded from the analysis
* only include patients randomised to testosterone 1% gel.
** for naïve indirect comparison
† The study was randomised and blinded in respect to dose of testosterone 1% gel from day 0-90. However, the results used in the naïve indirect comparison were from the non-randomised, open-label phase of the study (day 91-180)
Source: compiled during the evaluation based on Sections 2.1-2.4 of the submission.

6.8 The naïve indirect comparison was subject to uncertainty and the key transitivity issues are summarised below:

- Serum testosterone level at screening: patients in Study 127 had a higher serum testosterone level at screening (7.8 nmol/L) than those included in Swerdloff 2000 (6.4 nmol/L);
- Causes of hypogonadism: the majority of patients in the testosterone 1% gel arms of Swerdloff 2000 had established primary (40%) or secondary (20%) hypogonadism, while, as explained above, the underlying causes of androgen deficiency in Study 127 were not clear;
- Different assay methods were used to measure serum testosterone concentrations in the two studies (liquid chromatography-mass spectrometry/mass spectrometry assay in Study 127 versus radioimmunoassay in Swerdloff 2000), which may have contributed to the differences in the observed baseline testosterone levels and also confounded the measurement of response rate;
- Differences between studies in terms of the timepoint for assessment of response: 90 days for Study 127, and 180 days for Swerdloff 2000.

6.9 The submission did not specify a non-inferiority margin (minimal clinically important difference) for the outcome used in the naïve indirect comparison.

Comparative effectiveness

6.10 The pharmacokinetics of the two testosterone gel preparations at steady state differed, with diurnal variation in serum testosterone levels evident with testosterone 2% EP gel, while the serum concentrations remained fairly stable over 24 hours with testosterone 1% gel. The implications of these differences on the patient relevant clinical outcomes of resolution of symptoms, signs and complications of androgen deficiency were uncertain. The PSCR stated that as patients experience a variety of

symptoms associated with androgen deficiency, there is no single symptom that can be used to assess clinical improvement on a population basis. It noted that patient reported outcomes (erectile dysfunction, fatigue and general health) were recorded in Study 127 and that treatment with 2% gel was associated with improvements in all the patient reported outcomes. The PSCR noted that the presented responder analyses, defined as the proportion of patients who achieve testosterone concentration within the eugonadal range, was the efficacy outcome that could be compared between Study 127 and Swerdloff et al., 2000 and is consistent with the goal of TRT. Further, the PSCR stated that the PBAC has previously recommended TRTs on the basis of the achievement of testosterone levels within the eugonadal range (Axiron PSD, November 2011; AndroForte PSD, March 2015).

6.11 For the naïve indirect comparison, the submission used the response rate in the per protocol (PP) completers analysis set in Study 127, as it was considered that this analysis set best matched the analysis set for which the response rate was reported in Swerdloff 2000. The analysis set used for the response rate reported for Swerdloff 2000 included patients who received testosterone 1% gel from day 90-180 (the unblinded part of the study) and who had sufficient data for analysis at day 180 (i.e. completed the study).

6.12 While the conclusion was reasonable that the PP completer analysis set in Study 127 most closely resembled that used for the analysis of the response rate in Swerdloff 2000, a considerable proportion of patients in both studies were excluded from this analysis (Table 4). As the response rate in Swerdloff 2000 was not reported for any alternative analysis sets, a comparison of the response rates based on alternative analysis sets was not feasible, even though the PP completer analysis response rates were the least conservative from Study 127.

6.13 The response rates across the single arms in Study 127 and Swerdloff 2000 are summarised below.

Table 4: Results of the naïve indirect comparison of response rates for Study 127 and Swerdloff 2000.

	Testosterone 2% EP gel day 90 (Study 127)			Testosterone 1% gel day 180 (Swerdloff 2000)
	FAS§	**ITT with LOCF**	**PP population$^{\Psi}$**	***Completers****
Proportion of responders♦, n (%) [95% CI]	LOCF 118/155 (76.1) [69.4, 82.8] Completers^ 114/139 (82.0) [75.6, 88.4]	118/159 (74.2) *[67.4, 81.0]*	LOCF 114/145 (78.6) *[71.9, 85.3]* **Completers^** **111/134 (82.8)** **[76.5, 89.2]**	**112/129 (87)**† ***[81.0, 92.7]***
Average dose (mg/day)	NR	NR	60.07△	75.78†

Abbreviations: EP = enhanced permeation; FAS = full analysis set; ITT = intention to treat; LOCF = last observation carried forward; n = number of responders; N = total patients in the group; NR = not reported; PP = per protocol

§ The FAS included subjects who had sufficient pharmacokinetic data to determine an average total serum testosterone concentration (0-24 hours) on days 14, 35, 56 or 90. The primary analysis specified in the study protocol was the FAS analysis with LOCF.

$^{\Psi}$ The per protocol (PP) completers analysis set was defined as all FAS patients who completed the study and who did not have major protocol deviations that could affect the pharmacokinetic data.

^ Patients in the FAS or PP population who completed the study without LOCF imputation

***** The analysis set used for the response rate reported for Swerdloff 2000 included patients who received testosterone 1% gel from day 90-

180 and who had sufficient data for analysis at day 180 (i.e. completed the study).
† Calculated from the proportion of patients in each dose group at day 180. 140/151 (92.7%) of patients randomised to testosterone 1% gel continued into the day 91-180 phase of the study, and 3 patients initially assigned to the testosterone patch switched to 1% gel at day 91. 129/143 (90.2%) of patients receiving testosterone 1% gel from day 91-180 had sufficient data at day 180 (50 mg: n = 44, 75 mg: n = 37; 100 mg: n = 48
Δ Calculated from PP completer population. This included 134/160 (83.8%) of randomised patients (23 mg n = 5; 46 mg n = 45; 69 mg n = 89).
♦The definition of response rate was the proportion of responders in the target eugonadal testosterone range: Study 127 (17.3 – 36.4 nmol/L;) and Swerdloff 2000 (10.4 – 34.7 nmol/L).
Figures in italics calculated during the evaluation using STATA (Wald confidence interval).
Bolded figures indicate the results used in the indirect comparison presented in the submission.
Source: Table 2.6-1, p67, and Table 2.5-3, p54 of the submission, and CSR of Study 127 p63.

6.14 The submission concluded that the naïve indirect comparison showed that testosterone 2% EP gel was non-inferior to testosterone 1% gel for the outcome of response, defined as the proportion of patients with total testosterone average concentration over 24 hours ($C_{avg(0-24)}$) within the normal physiological range. The ESC agreed that this claim is subject to some uncertainty, due to the nature of the naïve indirect comparison (no common reference arm used) and transitivity concerns between Study 127 and Swerdloff 2000, but considered that overall the claim of non-inferiority of testosterone 2% EP gel to testosterone 1% gel was reasonable.

6.15 The results observed from Study 127 and Swerdloff 2000 may be of limited applicability to the proposed PBS population:

- As noted above, it was not clear how many of the patients in the key clinical studies would have met the criteria for PBS-subsidised treatment under the requested restrictions;
- The doses and titration of testosterone 1% gel in Swerdloff 2000 were not consistent with the approved product information (PI) of testosterone 1% gel. The PI recommends initiating treatment at 50 mg/day, with dose adjustment by 25 mg steps, to a maximum of 100 mg/day. In Swerdloff, patients were initiated at either 50 mg/day or 100 mg/day and only one dose adjustment at 90 days was allowed; patients receiving 50 mg/day were titrated to a maximum dose of 75 mg/day, while patients receiving 100 mg/day could only have their dose decreased to 75 mg/day. Therefore, patients receiving either 75 mg/day or 100 mg/day over days 91-180 (92/143, 64%) may still not have been adequately titrated. In addition, three patients initially randomised to the testosterone patch were switched to testosterone 1% gel 50 mg/day and did not undergo any dose titration. It is possible that a considerable proportion of patients may not have been receiving an optimally titrated dose of testosterone 1% gel.
- The median body mass index (BMI) in Study 127 was 31.0 kg/m^2, indicating that over 50% of patients in the study were obese[7]. Patient with androgen deficiency

[7] The World Health Organisation defines obesity as a BMI greater than or equal to 30. http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

due to obesity are not eligible for testosterone treatment under the proposed restriction for adult patients without established pituitary or testicular disorders.

Comparative harms

6.16 Adverse events (AEs) over 120 days for the intention to treat (ITT) population in Study 127 are summarised below.

Table 5: Adverse events reported by Study 127 over 120 days

	Patients, n (%) N = 159§	Events, n
All TEAEs	59 (37.1)	119
Mild/ moderate AEs	59 (37.1)	114
Severe AEs	4 (2.5)	5
Serious AEs	5 (3.1)	5
AE*	24 (15.1)	35
Withdrawal from study due to AEs,	7 (4.4)	-

Abbreviations: AEs = adverse events; n = number of patients experiencing an event; N = total patients in the group; TEAEs = treatment emergent adverse events.
§ Intent to treat (ITT) population with last observation carried forward (LOCF).
*Possibly or probably related to treatment.
Source: Table 2.5-12, p62 of the submission.

6.17 There was one serious adverse event (SAE) considered possibly related to testosterone 2% EP gel – myocardial infarction with stent placement. Twenty four patients experienced 35 AEs that were considered treatment related; the most commonly occurring AEs were erythema in four (2.5%), and blood triglycerides and prostate-specific antigen (PSA) each increased in two (1.3%) patients.

6.18 The PI for testosterone 2% EP gel states that androgens may accelerate the progression of prostate cancer and benign prostatic hyperplasia (BPH). Patients with an elevated or history of elevated PSA, a prostate exam suspicious for a malignancy or with prostate cancer were excluded from Study 127.

6.19 The TGA Clinical Evaluation Report for testosterone 2% EP gel (April 2017), reported that, while the safety analysis was consistent with the known profile of testosterone, the risk assessment was based on a small number of studies of short duration, with the inability to identify uncommon AEs, as well as long term known side effects such as gynaecomastia.

6.20 The submission stated that the discontinuations due to AEs was the only safety outcome that could be compared between testosterone 2% EP gel and 1% gel. In Study 127, 7/159 (4.4%) patients discontinued testosterone 2% EP gel due to an AE, of which 4 were considered to have a reasonable possibility of being related to study treatment (p87 Study 127 CSR). The submission reported that 11/151 (7.3%) patients discontinued testosterone 1% gel due to an AE by day 90 in Swerdloff 2000. This result could not be located in Swerdloff 2000. The US Food and Drug Administration (FDA) Medical Review for testosterone 1% gel reported that only six patients receiving testosterone 1% gel in Swerdloff 2000 experienced AEs associated with premature

discontinuation, with four considered possibly related to study drug (p23, FDA Medical Review, NDA 21-015)[8].

6.21 Given the lack of comparable data, and the transitivity concerns outlined above, no conclusion could be made in terms of the comparative safety of testosterone 2% EP gel versus testosterone 1% gel. The PSCR argued that "although testosterone 2% EP gel is formulated to promote enhanced permeation, the active drug remains unchanged" and that "the safety profile of testosterone is well-characterised as TRT have been used for the treatment of androgen deficiency for over 60 years" (Conway et al., 2000). The ESC noted that as the two formulations contain the same drug, any difference in comparative harms is likely to be dose dependent.

6.22 During the evaluation the absence of any data assessing the safety of testosterone 2% EP gel in patients under the age of 18 years was noted, despite three proposed PBS listings for patients in this population subgroup.

Clinical claim

6.23 The submission described testosterone 2% EP gel as non-inferior to testosterone 1% gel in terms of effectiveness and safety.

6.24 The ESC and PBAC acknowledged the concerns raised in the evaluation (outlined below) regarding the claim of non-inferiority of testosterone 2% EP gel to testosterone 1% gel, but considered that that the effectiveness of testosterone products is dependent on level and timing of drug absorption, and that the efficacy and safety issues raised in the evaluation are likely related to dose. As such, the ESC and PBAC considered that the claim of non-inferiority of testosterone 2% EP gel to testosterone 1% gel was reasonable.

6.25 Concerns raised in the evaluation regarding the claim of non-inferiority:

- The claim was based on a naive indirect comparison;
- The claim of non-inferiority compared to testosterone 1% gel in terms of effectiveness was based entirely on pharmacokinetic outcomes;
    - The submission did not present a comparison of the most relevant clinical outcomes such as resolution of symptoms, signs and complications of androgen deficiency;
    - Given the difference in the pharmacokinetics of the two preparations, it was not clear whether a comparison of the average testosterone concentration over 24-hours adequately captured the differences between the two

[8] Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-015_AndroGel.cfm

preparations, or whether this measure is a valid surrogate for clinically relevant outcomes;

- There were considerable transitivity issues between the two studies used in the naïve indirect comparison, especially in terms of the underlying causes of androgen deficiency, serum testosterone levels at screening, analytical methods used to measure serum testosterone concentrations, and the definition of the outcomes (serum testosterone eugonadal range and the time point for assessment of response);
- Due to the limited dose titration allowed in the key testosterone 1% gel study, Swerdloff 2000, it is possible that a considerable proportion of patients may not have been receiving the appropriate dose. This may have underestimated the response rate that would have been observed if all patients had been optimally titrated;

6.26 There was a lack of longer term efficacy and safety data (particularly around prostate dysfunction and cardiovascular health) for testosterone 2% EP gel. This is particularly relevant given that the treatment is indicated for chronic use.

Economic analysis

6.27 The submission presented a cost-minimisation analysis of testosterone 2% EP gel compared with testosterone 1% gel, based on the non-inferiority claim of these two medicines. The equi-effective doses are estimated as testosterone 2% EP gel 60.07 mg testosterone/day and testosterone 1% gel 75.78 mg testosterone/day, based on the naïve indirect comparison presented above. The ESC noted that there was some uncertainty in the estimated equi-effective doses of testosterone 2% EP gel and testosterone 1% gel versus the trials, given the nature of the naïve indirect comparison, the key transitivity concerns across the studies, and the uncertain applicability to the proposed PBS population.

6.28 There was some uncertainty regarding the dose of testosterone delivered by each actuation of the pump in the multidose bottles use in Swerdloff 2000. The publication stated that each actuation delivered 2.27 g of 1% gel (22.7 mg of testosterone per actuation), with patients in the 50 mg/day, 75 mg/day and 100 mg/day groups receiving 2, 3 or 4 actuations of active gel per day. This would mean that patients were actually receiving 45.4 mg, 68.1 mg or 90.8 mg of testosterone per day, respectively (p4501 'T gel and patch', Swerdloff 2000). The revised estimation of the average daily dose of testosterone 1% gel, and the results of the cost-minimisation based on this re-estimate have been presented in Table 6 and Table 7, respectively. The Pre-PBAC Response noted that the 22.7 mg testosterone per actuation is greater than 90% of the labelled dose (25 mg) which is within the specifications required for gel products per the 'Uniformity of Dosage Units'.

6.29 The study populations differed considerably in regard to the distribution of underlying causes of androgen deficiency. The submission did not present any evidence assessing

whether the comparative effectiveness and equi-effective doses were similar across these subgroups, or whether they were applicable to the proposed patient populations that were not included in the studies.

Table 6: Equi-effective doses of testosterone 2% EP gel and testosterone 1% gel.

Time point	Response, n	Response, % (95% CI)	Patients on each dose, n (%)			Average dose (mg)
			23 mg	46 mg	69 mg	
Study 127						
PP- completer[§]						
Day 90	N = 134 111	82.8 (76.5, 89.2)	5 (3.7)	42 (31.3)	87 (64.9)	60.07
Swerdloff 2000 [5] as provided in the submission						
Day 180	N = 129 112	87 (NR, NR)	**50 mg** 44 (34)	**75 mg** 37 (29)	**100 mg** 48 (37)	75.78
Swerdloff 2000 [5] Revised^						
Day 180	N = 129 112	87 (NR, NR)	**45.40 mg** 44 (34)	**68.10 mg** 37 (29)	**90.80 mg** 48 (37)	68.80

Abbreviations: CI = confidence interval; n = number of patients who responded; N = total number of patients; NR = not reported; PP = per protocol

[§] PP completer = patients who completed the study without major protocol deviation

^ Revised data based on patients receiving 45.4 mg and 90.8 mg instead of 50 mg and 100 mg testosterone 1% gel daily.

Source: Table 3.2-1, p79 & Table 3.2-2, p80 of the submission.

6.30 The ESC noted that there was some uncertainty in the estimated equi-effective doses of testosterone 2% EP gel and testosterone 1% gel. Based on the evidence presented in the submission, there are a number of alternatives for the equi-effective dose as outlined below:

- 60.07 mg 2% EP gel = 84 mg 1% gel based on bioavailability (equivalent to 1: 1.40);
- 60.07 mg 2% EP gel = 75.78 mg 1% gel based on indirect trial comparison (1:1.26);
- 60.07 mg 2% EP gel = 68.80 mg 1% gel based on indirect trial comparison with 1% dose based on dose delivered per actuation (1:1.15); and
- 23 mg 2% = 25 mg (2 x 12.5 mg) 1% based on doses delivered per pump actuation (1:1.09).

6.31 The PSCR acknowledged there are limitations in using a naïve comparison to derive the equi-effective doses, but argued that the equi-effective doses presented in the submission were supported by the head-to-head pharmacokinetic study (Study CS02), which showed that "the bioavailability of testosterone from testosterone 2% EP gel was 1.4-fold higher than that from testosterone 1% gel when the same dose (50 mg/day) was applied to for seven days." The PSCR stated that when the bioavailability ratio of 1.4 was applied to the average dose at the end of Study 127 (60.07 mg), this corresponded to 84 mg testosterone from testosterone 1% gel, which is similar to the 75.78 mg from the equi-effective dose derived from the naïve comparison.

6.32 The ESC considered that equi-effective doses of 23 mg 2% EP gel and 25 mg (2 x 12.5 mg) 1% gel may be appropriate noting that there is not always a direct relationship

between serum testosterone level and physiological response. The ESC also noted that higher doses may be used in practice versus trials.

6.33 The Pre-PBAC Response noted the equi-effective doses of currently listed TRTs have been based on clinical evidence demonstrating similar increases in testosterone levels. It was further noted in the Pre-PBAC Response that the goal of treatment is to restore eugonadal testosterone levels and the claim of non-inferior efficacy was based on similar proportions of patients in Study 127 and Swerdloff 2000 achieving testosterone levels within the eugonadal range.

6.34 The PBAC considered that the equi-effective doses of 60.07 mg 2% EP geland 75.78 mg 1% gel were consistent with the trial data and approach used previously to determine equi-effective doses.

6.35 No additional costs or cost offsets were considered relevant for inclusion in the cost-minimisation analysis. This is reasonable.

6.36 The results of the cost-minimisation analysis are summarised below.

Table 7: Results of cost-minimisation analysis of testosterone 2% EP gel compared with testosterone 1% gel.

Component	Testosterone 2% EP gel	Testosterone 1% gel
Maximum quantity	1,288 mg	1,500 mg
Weighted daily average dose Revised*	60.07 mg	75.78 mg 68.80 mg
Doses per pack Revised*	21.44	19.79 21.80
Costs based on EMP		
EMP	$[redacted] $[redacted]	$60.92
Cost per dose Revised*	$3.08 $2.79	$3.08 $2.79
Total medicine cost per week Revised*	$21.54 $19.56	$21.54 $19.56
Difference in cost per week	$0	$0
Cost per year Revised*	$1,123.35 $1,019.88	$1,123.35 $1,019.88
Costs based on DPMQ		
DPMQ Revised*	$[redacted] $[redacted]	$76.59
Total medicine cost per week Revised*	$[redacted] $[redacted]	$27.09 $24.59
Cost per year Revised*	$[redacted] $[redacted]	$1,412.33 $1,282.24

Abbreviations: DPMQ = dispensed price for maximum quantity; EMP = ex-manufacturer price; EP = enhanced permeation

* Figures in italics were calculated using the average dose for testosterone 1% gel calculated in Table 6 assuming that the pump in the multi-dose bottles used in Swerdloff 2000 dispensed 22.7 mg of testosterone per actuation.

Source: Table 3.4-2, p84 of the submission; Excel workbook 'TESTAVAN (testosterone) Section 3.xlsx.'

Drug cost/patient/year: $[redacted]

6.37 This was based on the estimated dispensed price for maximum quantity (DPMQ) of $[redacted] for a pump pack dispensing 1,288 mg of testosterone (56 metered doses, each containing 23 mg of testosterone), which is sufficient for, on average, 21.4 days of

therapy. This compared to a cost of $1,412.33/patient/year for testosterone 1% gel, based on the DPMQ of $76.59 for 1 pump pack dispensing 1,500 mg testosterone (12.5 mg testosterone per pump actuation, 2 x 60 actuations), which is sufficient, on average for 19.8 days of therapy.

Estimated PBS usage & financial implications

6.38 This submission was not considered by DUSC.

6.39 The submission took a market share approach to estimate the use of testosterone 2% EP gel, should it be listed on the PBS.

6.40 The submission used an ex-manufacturer price (EMP) of $[redacted] for testosterone 2% EP gel (DPMQ $[redacted]), rather than the EMP of $[redacted] (DPMQ $[redacted]) derived in the cost-minimisation analysis presented in the submission. The financial implications were recalculated during the evaluation, using an EMP of $[redacted] for testosterone 2% EP gel, and the results are presented in Table 8.

6.41 The estimated use and financial implications of listing testosterone 2% EP gel are summarised below.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of testosterone 2% EP gel						
Cost to PBS/RPBS * Revised	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments * Revised	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Estimated financial implications for testosterone 1% gel and 5% cream						
Saving to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Saving to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS * Revised	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]

Abbreviations: EP = enhanced permeation

* Revised assuming a DPMQ of $[redacted] for testosterone 2% EP gel, as derived in the cost-minimisation analysis.

Source: Table 4.4-1, p95 of the submission

The redacted table shows that at Year 6, the estimated number of scripts was 10,000-50,000 per year and the net cost to the PBS/RPBS would be $10 – $20 million in year 6.

6.42 The submission estimated a net cost to the PBS/RPBS of $[redacted] (revised: $[redacted]) in year 1, increasing to $[redacted] ($[redacted]) in year six, due to the difference in pack size and the consequent difference in patient copayments. Testosterone 2% EP gel, due to its double strength formulation, and hands free applicator may increase compliance

compared to testosterone 1% gel, resulting in more prescriptions per patients per year.

6.43 The submission stated that a listing for testosterone 2% EP gel on the PBS was not expected to result in additional resource use such as tests, procedures or visits to healthcare professionals, and therefore no change in the cost to the Medicare Benefits Scheme (MBS) was expected.

Quality Use of Medicines

6.44 In July 2014, PBAC amended PBS restrictions for testosterone products to minimise their use beyond the PBS restriction, based on outcomes of a DUSC review (Item 4.1 testosterone PSD, July 2014 PBAC Meeting).

6.45 While not quantified, ESC considered that there may be a quality use of medicines advantage of a topical testosterone product that is absorbed faster, as this could reduce the potential for inadvertent drug transfer to non-patients.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (telephone) listing of testosterone 2% enhanced permeation (EP) gel for the treatment of androgen deficiency. The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost effectiveness of testosterone 2% EP gel would be acceptable if it were cost-minimised against the currently listed testosterone 1% gel.

7.2 The PBAC noted that the submission was based on a naïve indirect comparison between two studies: (1) Study 127 (N=159), an open-label single arm study evaluating the efficacy and safety of testosterone 2% EP gel in adult men with androgen deficiency; (2) Swerdloff 2000 (N=227) a three arm randomised trial in hypogonadal men where patients were randomised to receive either one of two doses (50 mg or 100 mg testosterone/day) of testosterone 1% gel or a testosterone patch.

7.3 While the PBAC acknowledged the uncertainty of the naïve indirect comparison and transitivity issues between the two studies, the PBAC considered that overall, the claim of non-inferior efficacy compared with testosterone 1% gel was reasonable. The PBAC noted that the issues in regards to the relative safety and efficacy raised by the evaluation are likely related to dose as the efficacy of testosterone products are dependent on the level and timing of testosterone absorption.

7.4 The PBAC noted that there was uncertainty regarding the equi-effective doses for the 2% EP gel and 1% gel. The PBAC considered the dose of the 1% gel as reported in Swerdloff 2000 was within the requirements as per the 'Uniformity of Dosage Units' specification, therefore the PBAC considered it appropriate for the equi-effective doses to be based on the trial data as it was consistent with the approach generally

used, including for previous TRTs. As such, the PBAC considered that the equi-effective doses are:

- 60.07 mg testosterone of the 2% EP gel and 75.78 mg testosterone of the 1% gel.

7.5 The PBAC considered that the 2% EP gel presentation of testosterone may be useful for some patients due to the shorter absorption time.

7.6 The PBAC recommended the listing of the testosterone 2% EP gel for the same conditions as the currently listed testosterone products.

7.7 The PBAC advised that testosterone 2% EP gel is not suitable for prescribing by nurse practitioners.

7.8 The PBAC recommended that the Early Supply Rule should apply.

7.9 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:

Name, Restriction, ***Manner of administration and form***	**Max. Qty**	**№.of Rpts**	**Proprietary Name and Manufacturer**
TESTOSTERONE 2% (23 mg/actuation) gel, 56 actuations	1	5	Testevan® Ferring Pharmaceuticals Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Androgen deficiency
PBS Indication:	Androgen deficiency
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined

Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Clinical criteria:	Patient must have an established pituitary or testicular disorder
Administrative Advice (not included in LI)	The name of the specialist must be included in the authority application

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Androgen deficiency
PBS Indication:	Androgen deficiency
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Clinical criteria:	Patient must not have an established pituitary or testicular disorder AND The condition must not be due to age, obesity, cardiovascular diseases, infertility or drugs
Population criteria:	Patient must be aged 40 years or older
Prescriber Instructions:	Androgen deficiency is defined as: i) testosterone level of less than 6 nmol per litre; OR ii) testosterone level between 6 and 15 nmol per litre with high luteinising hormone (LH) (greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14 IU per litre, whichever is higher) Androgen deficiency must be confirmed by at least two morning blood samples taken on different mornings. The dates and levels of the qualifying testosterone and LH measurements must be, or must have been provided in the authority application when treatment with this drug is or was initiated
Administrative Advice (not included in LI)	The name of the specialist must be included in the authority application

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Micropenis
PBS Indication:	Micropenis
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Population criteria:	Patient must be under 18 years of age
Administrative Advice (not included in LI)	The name of the specialist must be included in the authority application

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Pubertal induction
PBS Indication:	Pubertal induction
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Population criteria:	Patient must be under 18 years of age
Administrative Advice (not included in LI)	The name of the specialist must be included in the authority application

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Constitutional delay of growth or puberty
PBS Indication:	Constitutional delay of growth or puberty
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.
Population criteria:	Patient must be under 18 years of age
Administrative Advice (not included in LI)	The name of the specialist must be included in the authority application

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.