

5.23 TESTOSTERONE

50mg/mL (5%w/v), cream, 50mL;

AndroForte 5®; Lawley Pharmaceuticals Pty Ltd.

1 Purpose of Application

1.1 Authority Required listing for testosterone 5% (w/v) cream, AndroForte 5®, for the treatment of androgen deficiency. This product is a new formulation of topical testosterone; three topical transdermal formulations are currently listed for the same patient population – solution, patch and gel.

2 Requested listing

- 2.1 Androgen deficiency in:
- a) Males with established pituitary or testicular disorders
 - b) Males aged 40 year or older where androgen deficiency is demonstrated through hormone levels
 - c) Males aged under 18 years with micropenis, delayed puberty or constitutional delay of growth or puberty.

Name, Restriction, Manner of administration and form	Max. Qty	Ne.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TESTOSTERONE Cream 50mg/mL (w/v) 5%, 50mL	1	6	\$ [REDACTED]	AndroForte 5 Lawley Pharmaceuticals

Authority required

2.2 At its July 2014 meeting, the PBAC recommended amendments to the Authority Required restrictions for testosterone products. These revised restrictions came into effect for all PBS listed testosterone products on 1 April 2015 and are described below.

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Restriction 1	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Androgen deficiency
Treatment criteria:	Must be treated by or in consultation with a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; <i>or in consultation with one of these specialists</i> ; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have an established pituitary or testicular disorder
Population criteria:	Patient must be male
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 2	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Androgen deficiency
Treatment criteria:	Must be treated by or in consultation with a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; <i>or in consultation with one of these specialists</i> ; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> 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 male AND Patient must be aged 40 years or older

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Prescriber Instructions	<p>Androgen deficiency is defined as:</p> <p>i) testosterone level of less than 6 nmol per litre; OR</p> <p>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)</p> <p>Androgen deficiency must be confirmed by at least two morning blood samples taken on different mornings.</p> <p>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</p>
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 3a	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Micropenis
Treatment criteria:	Must be treated by or in consultation with a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; <i>or in consultation with one of these specialists</i> ; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Population criteria:	<p>Patient must be male</p> <p>AND</p> <p>Patient must be under 18 years of age</p>
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 3b	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Pubertal induction
Treatment criteria:	Must be treated by or in consultation with a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; <i>or in consultation with one of these specialists</i> ; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

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Population criteria:	Patient must be male AND Patient must be under 18 years of age
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 3c	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Constitutional delay of growth or puberty
Treatment criteria:	Must be treated by or in consultation with a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; <i>or in consultation with one of these specialists</i> ; or have an appointment to be assessed by one of these specialists.
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Population criteria:	Patient must be male AND Patient must be under 18 years of age
Administrative Advice	The name of the specialist must be included in the authority application

- 2.3 The submission proposed listing on the PBS on the basis of a single bioequivalence trial comparing testosterone 5% cream and testosterone 1% gel and cost-minimisation to the currently listed testosterone 1% gel.

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

3 Background

- 3.1 **TGA status:** Testosterone 5% (50mg/mL), 50mL, AndroForte 5, was TGA registered on 11 July 2014 for testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.
- 3.2 This product was first submitted to the TGA in 2005. Following further consultation additional information was provided (the study presented in this submission) in 2012. The delegate rejected approval in January 2014. Following a Section 60 appeal, the TGA delegate granted approval on 30 May 2014.

4 Clinical place for the proposed therapy

- 4.1 The clinical signs and symptoms of androgen deficiency include reduced muscle strength, regression of secondary sexual characteristics, osteoporosis, fatigue, reduced libido, erectile dysfunction and mood changes.
- 4.2 Hypogonadism can be categorised as primary or secondary and the causes may be congenital or acquired. Primary hypogonadism occurs as a result of testicular failure. Congenital causes include Klinefelter and Prader-Willi syndromes and congenital anorchidism, whereas acquired testicular failure can be caused by alcoholic liver cirrhosis or systemic disorders such as haemochromatosis. Secondary hypogonadism occurs as a result of hypothalamo-pituitary axis failure resulting from conditions such as pituitary tumours and Kallman's Syndrome. Other acquired causes of primary and secondary hypogonadism include trauma, testicular torsion, orchitis, radiation or chemotherapy.
- 4.3 Ageing is also associated with a decline in testosterone levels, with typically an annual decline in total and free testosterone of 1.0% and 1.2% respectively after 40 years of age. The incidence of hypogonadism is increased in patients with Type 2 diabetes and metabolic syndrome.
- 4.4 The submission proposed that the place in therapy of testosterone cream is as an alternative therapy to testosterone transdermal gel for androgen deficiency in males.

5 Comparator

- 5.1 The submission proposed testosterone 1% gel (Testogel®). This is the appropriate comparator.

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 was based on one head-to-head crossover trial comparing testosterone 5% cream and testosterone 1% gel (n=16).
- 6.4 Details of the trial presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
LP101	Bioequivalence study comparing AndroForte 5 and Testogel 1%	Unpublished

Source: Appendix 13 of the submission

6.5 The key features of the direct randomised trial are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Testosterone 5% cream compared to testosterone 1% gel					
LP 101	16	R, crossover, single centre, OL, 60 days	Low	Androgen deficiency	Pharmacokinetic measures

OL=open label; R=randomised.

Source: compiled during the evaluation

6.6 The purpose of the trial was to provide evidence of bioequivalence. The primary outcome measures for bioequivalence are the area under the curve from 0-24 hours (AUC), maximum observed serum testosterone concentration (C_{max}), time to maximum serum concentration C_{max} (T_{max}), percentage fluctuation in serum concentrations and serum half-life ($T_{1/2}$).

Comparative effectiveness

6.7 The TGA delegate determined that ‘AndroForte and Testogel are therapeutically equivalent for all practical purposes’. This was supported by the unadjusted results of the primary outcomes of trial LP101. The estimated ratios of treatment effect, using Testogel as the reference product are presented below. Both the unadjusted and baseline adjusted results are presented.

Unadjusted results for the primary pharmacokinetic factors

Variable	Day	Ratio	Lower 90% CI	Upper 90% CI
AUC	1-2	1.05	0.91	1.2
AUC	30-31	1.01	0.85	1.19
Cmax	1-2	1.08	0.92	1.27
Cmax	30-31	1.03	0.85	1.25
Cavg	1-2	1.05	0.91	1.2
Cavg	30-31	1.01	0.85	1.19

Source Table B-17 submission, JWCS Expert Report Attachment 14

Baseline adjusted results for the primary pharmacokinetic factors

Variable	Day	Ratio	Lower 90% CI	Upper 90% CI
AUC	1-2	1.06	0.92	1.24
AUC	30-31	0.94	0.81	1.09
Cmax	1-2	1.1	0.91	1.31
Cmax	30-31	0.99	0.8	1.21
Cavg	1-2	1.06	0.92	1.24
Cavg	30-31	0.94	0.81	1.09

Source Table B-18 submission, JWCS Expert Report, Attachment 14

Baseline is defined as the average of the three readings prior to treatment on days 1 and 30.

AUC= area under curve; Cmax= maximum concentration; Cavg= average concentration; CI= confidence interval

Comparative harms

6.8 There was no difference in harms between the testosterone products.

Clinical claim

6.9 The submission described testosterone 5% cream as bioequivalent in terms of comparative pharmacokinetic measures to testosterone 1% gel. The submission assumed that the product was also non-inferior to testosterone 1% gel in terms of comparative effectiveness and comparative safety.

6.10 The TGA delegate considered that the sponsor provided “satisfactory evidence to establish quality, safety and efficacy of testosterone 5% cream for its intended use”, and concluded that AndroForte and Testogel are “essentially bioequivalent”. However, the evaluation considered that the claim of non-inferiority may not be adequately supported because of the reliance on an inappropriate trial design to support a conclusion of non-inferior comparative effectiveness.

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

Economic analysis

6.11 The submission presented a cost-minimisation analysis based on the doses used in Trial LP101. The equi-effective doses were estimated as testosterone 5% cream 100mg daily and testosterone 1% gel 50mg daily. Androgen replacement therapy is continuous and life-long. The equi-effective doses were appropriate if the claim of non-inferiority was accepted.

Comparison between Testogel and AndroForte 5

	Unit Pack	Recommended dose	# days' supply per Unit	PBS DPMQ	Cost/day	Rpts	Total days' supply including repeats
Testogel	30 x 5g sachets	One sachet daily	30	\$95.46	\$3.182	5	180
AndroForte 5	50ml	2ml daily	25	\$79.55	\$3.182	6	175

Submission page 74 corrected during the evaluation

Drug cost/year: \$1,161 calculated from 14.6 prescriptions at \$79.55 for 365.25 days per year.

Estimated PBS usage & financial implications

- 6.12 This submission was not considered by DUSC.
- 6.13 The submission used a market share approach based on analysis of pharmacy claim data collected by Medicare Australia. This was appropriate.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Market share	%	%	%	%	%
Scripts ^a					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS					
Net cost to MBS					
Estimated total net cost					
Net cost to PBS/RPBS/MBS					

^a Assuming 14.61 prescriptions per year as estimated by the submission (100% compliance).

Source: Table E.4 p77 of the submission/Excel workbook Attachment 19 Section E spreadsheets

- 6.14 The submission did not include testosterone 2% solution in its estimate of the size of the current testosterone market. If this was included there would have been a greater increase in the percentage market growth (calculated as 29.27% per annum compared to 14.55% per annum in the submission). Therefore the evaluation considered that the submission had underestimated the total number of prescriptions and cost of testosterone 5% cream per year to the PBS/RPBS. However the assumption of complete substitution of the cream for currently listed gel or solution was reasonable and the overall effect would remain zero assuming similar compliance to each product.
- 6.15 The growth rate for this market was uncertain. Analysis of the market for testosterone showed an overall increase in use but with large variation between different years in the growth of individual products. For this reason it was likely that the calculation of market growth, based on three years of data, had poor reliability.

Quality Use of Medicines

- 6.16 The PBAC had considered a range of issues regarding testosterone at its July 2014 meeting. The PBAC had reviewed the restrictions following the DUSC report and further consultation with clinical groups and pharmaceutical industry. The restriction wording resulting from this process is reflected in Section 2 'Requested listing' above.
- 6.17 The ESC noted that there may not be a compelling clinical need for another topical testosterone preparation noting that three topical formulations are currently listed for the same patient population – solution, patch and gel. Further, there is a potential for overuse of testosterone products. However, the ESC noted that the submission stated that testosterone cream has been available in Western Australia since 1999.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of testosterone 5% cream on a cost-minimisation basis with the currently listed testosterone 1% gel. The PBAC considered that the equi-effective doses are testosterone 5% cream 100 mg daily and testosterone 1% gel 50 mg daily.
- 7.2 The PBAC recommended the listing of testosterone 5% cream under the same conditions as the currently listed testosterone products.
- 7.3 The PBAC accepted that testosterone 1% gel was the appropriate comparator, as nominated in the submission.
- 7.4 The PBAC accepted that testosterone 5% cream is non-inferior to testosterone 1% gel, noting that the TGA delegate had considered that the sponsor provided “satisfactory evidence to establish quality, safety and efficacy of testosterone 5% cream for its intended use”, and the TGA delegate had concluded that AndroForte and Testogel are “essentially bioequivalent”.
- 7.5 The PBAC advised that testosterone cream is not suitable for prescribing by nurse practitioners.
- 7.6 The PBAC recommended that the Safety Net 20 Day Rule should apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
TESTOSTERONE Cream 50mg/mL (w/v) 5%, 50mL	1	6	AndroForte 5	Lawley Pharmaceuticals

Restriction 1	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Androgen deficiency
Treatment criteria:	Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member 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:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have an established pituitary or testicular disorder
Population criteria:	Patient must be male
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 2	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Androgen deficiency
Treatment criteria:	Must be treated by a specialist urologist, specialist endocrinologist or a registered member 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.

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> 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 male AND 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	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Micropenis
Treatment criteria:	Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member 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:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Population criteria:	Patient must be male AND Patient must be under 18 years of age
Administrative Advice	The name of the specialist must be included in the authority application

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Restriction 3b	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Pubertal induction
Treatment criteria:	Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member 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:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Population criteria:	Patient must be male AND Patient must be under 18 years of age
Administrative Advice	The name of the specialist must be included in the authority application

Restriction 3c	
Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Constitutional delay of growth or puberty
Treatment criteria:	Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member 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:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Population criteria:	Patient must be male AND Patient must be under 18 years of age
Administrative Advice	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.