

4.1 REVIEW OF PROPOSED AMENDMENTS TO PBS RESTRICTIONS FOR TESTOSTERONE PRODUCTS

1 Purpose of application

- 1.1 To advise the PBAC of responses from sponsors and stakeholders in relation to recommended amendments to the PBS restrictions for testosterone products from the August 2013 Special PBAC meeting.
- 1.2 To propose revised amended PBS restrictions for testosterone products that better clarify the intent of the Committee.

2 Requested listing

- 2.1 The PBAC noted that there are currently three separate PBS restrictions for testosterone products:

Restriction 1:

Authority required

Androgen deficiency in males with established pituitary or testicular disorders.

Restriction 2:

Authority required

Androgen deficiency in males 40 years and older who do not have established pituitary or testicular disorders other than aging, confirmed by at least 2 morning blood samples taken on different mornings. Androgen deficiency is confirmed by testosterone less than 8 nmol per L, or 8-15 nmol per L with high LH (greater than 1.5 times the upper limit of the eugonadal reference range for young men).

Restriction 3:

Authority required

Micropenis, pubertal induction, or constitutional delay of growth or puberty, in males under 18 years of age.

For more detail on PBAC's view, see section 5 "PBAC outcome"

3 Background

At its October 2012 meeting, DUSC reviewed the utilisation of PBS listed testosterone. The utilisation analysis highlighted the following key points:

- Utilisation of testosterone has doubled over the past 5 years.
- Expenditure has increased more than the growth in utilisation. This suggests that therapeutic relativities may require review.
- The listing of two products, testosterone gel and intramuscular injection 1000mg, have driven the growth in the market.
- There is a trend towards more GPs initiating therapy.
- There may be some use of testosterone that is not within the PBS restriction.
- There are some safety concerns with testosterone including possible increased cardiovascular risk in older men.

In its August 2013 consideration of the DUSC analysis report, the PBAC noted the following recent utilisation and expenditure trends regarding testosterone products:

- Increased expenditure in the last five years coincided with the PBS-listing of the transdermal gel and the long-acting intramuscular injection 1000mg.
- The number of PBS/RPBS-prescriptions increased, while non-PBS prescriptions remained stable and low.
- Though the proportion of GPs writing the first testosterone prescription for a patient has increased only slightly (62 % in 2005 to 68 % in 2011), almost all of the growth in new patients treated in the most recent year of analysis (2011) was due to initiations by GPs (84 %), rather than by specialists.
- Utilisation in the younger age groups remained constant, while initiations for patients aged 40-79 years had increased over time. The PBAC considered that the growth in initiations for patients in the 40-79 aged cohorts may be due to the increase in diagnosis and treatment of PBS listed indications, however may also include inappropriate use outside the PBS restrictions, such as patients without a pathologically-based androgen deficiency.

The PBAC made the following recommendations regarding the PBS restrictions for testosterone products:

- Amending the serum testosterone threshold for men aged 40 years or older who do not have established pituitary disorders to 6-15nmol/L in combination with a high LH (greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14 IU/L, whichever is higher). Confirmation of androgen deficiency should include measurement of serum testosterone, LH and FSH to allow for the appropriate diagnosis of primary androgen deficiency.
- Patients prescribed testosterone must be treated by a specialist paediatric endocrinologist, specialist paediatrician, specialist general paediatrician, specialist endocrinologist, specialist urologist, or a general practitioner in consultation with one of the above specialists listed or to have an appointment to be assessed by one of these specialists.
- Excluding treatment for low serum testosterone due primarily to age, obesity, cardiovascular diseases, infertility or drugs. These indications have not been assessed for efficacy and cost-effectiveness by the PBAC.

Some of the issues raised in responses to stakeholder consultation on the recommended changes include:

- Concern that the proposal to lower the defined testosterone threshold level is not consistent with international and Australian consensus guidelines, which define androgen deficiency according to the thresholds in the current restriction (less than 8 nmol/L or 8-15 nmol/L with high LH);
- Concern that the proposal to lower the defined testosterone threshold level is based upon a single cohort study of men aged 70-89 years and may not be applicable to the wider PBS population;
- Inappropriate application of testosterone threshold levels to the indication for patients with established pituitary or testicular disorders;
- Concern for the requirement for testosterone to be prescribed by or in consultation with specialists;
- Confusion regarding the requirement for the condition not to be due to age, obesity, cardiovascular diseases, infertility or drugs;
- Suitability for sexual health physicians to be included among those specialists by or in consultation with whom testosterone may be prescribed.

4 Consideration of the evidence

- 4.1 Following stakeholder consultation, the Secretariat undertook a further review of the proposed amendments to the restrictions and considered that they did not accurately reflect the intent of the PBAC. The Secretariat noted the following in its review:
- it is unnecessary to have separate initial and continuing treatment restrictions for treatment of patients with established pituitary or testicular disorders (Restriction 1) if there is no measure of response in order to qualify for continuing treatment;
 - reference to serum testosterone and LH thresholds should only be included in the restriction for men aged 40 years or older who do not have established pituitary or testicular disorders (Restriction 2);
 - the thresholds intended by the PBAC were serum testosterone of less than 6 nmol per L or serum testosterone 6-15 nmol per L with high LH, where high LH is defined as greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14 IU/L, whichever is higher;
 - the requirement for prescribing by or in consultation with nominated specialists should be restriction-specific: e.g. it would not be appropriate for patients aged 40 years and over to be treated by paediatric specialists.

For more detail on PBAC's view, see section 5 "PBAC outcome"

5 PBAC Outcome

- 5.1 The PBAC noted that the existing Restrictions 1 and 2 state that the condition (androgen deficiency) must not be due to age, obesity, cardiovascular diseases, infertility or drugs. The PBAC agreed with the Secretariat that this criterion is redundant for Restriction 1, where the condition for PBS eligibility is identified as being due to established pituitary or testicular disorders. The PBAC recommended the removal of this criterion from Restriction 1.
- 5.2 With regard to Restriction 1, the PBAC noted the Secretariat's request for advice on whether it is necessary to identify specific pituitary and testicular disorders for patients to be eligible for PBS-subsidy under this restriction. The PBAC considered that it was not necessary for specific disorders to be referred to in the restriction.
- 5.3 The PBAC noted the request from stakeholders to include specialist sexual health physicians among those specialists able to prescribe or be consulted on prescribing of PBS-listed testosterone products. The PBAC considered that a more appropriate definition would be "a registered member of the Australasian Chapter of Sexual Health Medicine". The PBAC recommended that this definition be included in all PBS restrictions for testosterone products.

Outcome:

Recommended

Following consideration of input from stakeholders and the Department, the PBAC recommended amending the restrictions for testosterone products to:

- For restrictions for androgen deficiency, remove redundant reference to the condition not being due to age, obesity, cardiovascular diseases, infertility or drugs;
- Include registered members of the Australasian Chapter of Sexual Health Medicine as prescribers that are able to prescribe testosterone products on the PBS.

6 Recommended listing

6.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
TESTOSTERONE				
testosterone 2% (30 mg/1.5 mL actuation) transdermal solution, 60 actuations	1	5	Axiron	EL
testosterone 2.5 mg/24 hours patch, 60	1	5	Androderm	GN
testosterone 5 mg/24 hours patch, 30	1	5	Androderm	GN
testosterone 1% (50 mg/5 g) gel, 30 x 5 g sachets	1	5	Testogel	BN
TESTOSTERONE ENANTHATE				
testosterone enanthate 250 mg/mL injection, 3 x 1 mL syringes	1	3	Primoteston Depot	BN
TESTOSTERONE UNDECANOATE				
testosterone undecanoate 40 mg capsule, 60	1	5	Andriol Testocaps	MK
testosterone undecanoate 1 g/4 mL injection, 1 x 4 mL ampoule	1	1	Reandron	BN

RESTRICTION 1	
Condition:	Androgen deficiency
Restriction:	Authority required
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 or have an appointment to be assessed by one of these specialists.
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	
Condition:	Androgen deficiency
Restriction:	Authority required

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Treatment criteria:	Must be treated by or in consultation with a specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine 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 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.
Prescriber instructions	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 3(a)

Condition:	Micropenis
Restriction:	Authority required
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 or have an appointment to be assessed by one of these specialists.
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 3(b)	
Condition:	Pubertal induction
Restriction:	Authority required
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 or have an appointment to be assessed by one of these specialists.
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 3(c)	
Condition:	Constitutional delay of growth or puberty
Restriction:	Authority required
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 or have an appointment to be assessed by one of these specialists.
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

7 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.

8 Sponsors' Comments

Actavis Pty Ltd: The sponsor has no comment.

Bayer Australia Limited*: The sponsor has no comment.

Besins Healthcare Australia Pty Ltd: The sponsor notes the DUSC review and the subsequent considerations by the PBAC were instigated to ensure appropriate prescribing of

testosterone replacement therapies by GPs and specialists. The sponsor considers that the requirement that treatment must be by or in consultation with a specialist may add an additional cost and time burden for GPs and patients.

Eli Lilly Australia Pty Limited^{**}: Eli Lilly welcomes the removal of unnecessary initial and continuing treatment restrictions, and reference to serum and testosterone and LH thresholds for patients with established pituitary or testicular disorders.

We are concerned that patients accessing treatment could incur delays by linking prescribing to confirmation of a speciality consultation, it is therefore important that in implementing these new restrictions the guidance is clear to prescribers.

Hospira Pty Ltd^{***}: The sponsor has no comment.

Merck Sharp & Dohme (Australia) Pty Ltd: The sponsor has no comment.

* Bayer Australia Pty Ltd was the sponsor of Testogel® at the time the utilisation analysis was considered by the DUSC in October 2012. Besins Healthcare Australia Pty Ltd took over as sponsor of this product on 1 October 2014.

** Eli Lilly Australia Pty Ltd did not have a testosterone product listed on the PBS at the time the utilisation analysis was considered by the DUSC in October 2012, however Axiron® had received a positive recommendation from the PBAC in March 2012 and was listed in March 2013.

*** Hospira Pty Ltd was the sponsor of Androderm® products at the time the utilisation analysis was considered by the DUSC in October 2012. Ascent Pharma Pty Ltd took over as sponsor of these products on 1 February 2013, and then Actavis Pty Ltd on 1 October 2013.