

## Item 3 – Testosterone

### 1 Purpose of Item

- 1.1 To provide the PBAC with the findings of the DUSC analyses of utilisation of testosterone.
- 1.2 For PBAC to consider if the PBS restrictions for testosterone products require revision.
- 1.3 For PBAC to consider if any revisions of the dose relativities for pricing purposes are required.

### 2 Background

- 2.1 At its October 2012 meeting, the DUSC reviewed the utilisation of PBS listed testosterone. The utilisation analysis was prompted by a research article highlighting an increase in Pharmaceutical Benefits Scheme (PBS)-subsidised testosterone prescribing<sup>1</sup>.
- 2.2 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.
- 2.3 Sponsors of all PBS-listed testosterone products and other stakeholders including Andrology Australia, the ANZAC Research Institute, the Endocrine Society of Australia, the Royal Australian College of General Practitioners (RACGP) and the Royal Australasian College of Physicians (RACP) were provided with the DUSC report and an opportunity to comment.

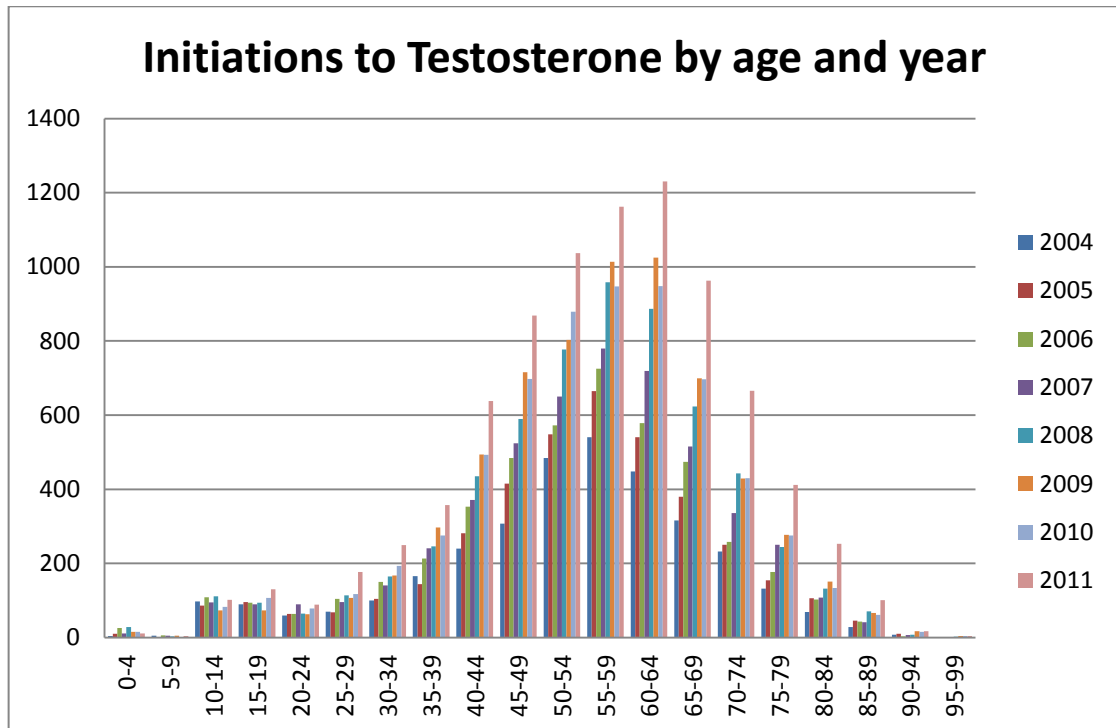
### 3 PBAC Discussion

- 3.1 The PBAC noted recent utilisation trends of testosterone products and the increased expenditure in the last five years coincided with the PBS-listing of the transdermal gel and the long-acting intramuscular injection 1000 mg.
- 3.2 The PBAC noted that 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), the PBAC noted that 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.

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<sup>1</sup> Handelsman DJ. Pharmacoepidemiology of testosterone prescribing in Australia, 1992–2010. *Med J Aust* 2012; 196 (10): 642-645. doi: 10.5694/mja11.11277.

- 3.3 The PBAC noted the utilisation in the younger age groups had remained constant, while initiations for patients aged 40-79 years had increased over time as shown below. 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.



- 3.4 The PBAC noted that the expenditure for testosterone had increased compared to the utilisation and the PBAC did not consider that there was any basis to revise the dose relativities for pricing purposes at this time.
- 3.5 The PBAC considered the safety concerns presented in the DUSC review and in the Basaria *et al* 2010 study. The PBAC noted the study was primarily based on elderly men and that observations were unlikely to be of significant concern when extrapolated to the use of testosterone in Australia.
- 3.6 The PBAC noted the original serum testosterone threshold was 8.0 nmol/L and was based on informed judgement from advice and correspondence from the Endocrine Society, the Australasian Paediatric Endocrine Group, sponsors at the time (Schering, Organon) and clinicians during the December 1998 and March 1999 PBAC meeting. This threshold was vindicated in recent studies (Sartorius *et al* 2012 Clin Endocrinol).
- 3.7 The PBAC noted recent Australian data that indicated a more appropriate serum testosterone threshold for prescribing testosterone in older men would be 6 nmol/L (Yeap *et al* 2012 J Clin Endocrinol Metab). This concentration was based on a large population cohort of healthy older men who have no symptoms that could be attributable to testosterone deficiency.
- 3.8 The PBAC acknowledged the concern raised by DUSC that a high degree of variability has been observed in the measurement of testosterone levels depending on the assay methodology used. The PBAC noted the challenges in clinical diagnosis

of testosterone deficiency and the accuracy in establishing a definitive threshold. Therefore, the PBAC noted the testosterone range of 6-15 nmol/L, in combination with a high LH and FSH concentrations, would address any issues of diagnostic variability, while still being consistent with current studies and international recommendations for diagnosis of androgen deficiency.

#### **4 PBAC Outcomes**

- 4.1 The PBAC recommended amending the serum testosterone threshold in the PBS restriction for men aged 40 years or older who do not have established pituitary disorders to 6-15 nmol/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. The PBAC noted that testing of serum LH and FSH together with serum testosterone is not expected to increase the cost to the Commonwealth as the MBS item 66695 already covers up to 6 assays from a single sample.
- 4.2 The PBAC recommended 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. The PBAC recommended that the Secretariat consult with the Australian Health Practitioner Regulation Agency (AHPRA) to ensure that the specialist prescribers nominated in the revised restriction are identified as such under national registration requirements, prior to implementing the revised restriction.
- 4.3 The PBAC recommended 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.
- 4.4 The PBAC recommended that a review of testosterone utilisation by DUSC to be undertaken twelve months after the PBS restriction has been finalised and implemented.
- 4.5 Noting the strong possibility of prescribing of testosterone outside the PBS restriction, the PBAC recommended that the Department refer this matter to the Compliance area of Department of Human Services for appropriate action.
- 4.6 The recommended restriction is considered complicated and will be finalised out of session.

#### **5 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.

#### **6 Sponsors' Comments**

Actavis Pty Ltd: The sponsor has no comment.

Bayer Australia Limited\*: The sponsor has no comment.

Besins Healthcare Australia Pty Ltd: Besins Healthcare Australia supports evidence based medicine and clinical best practice. The sponsor notes that the PBAC re-affirmed that the serum testosterone threshold of 8.0 nmol/L was 'vindicated in recent studies'. The sponsor notes that the new serum testosterone threshold for prescribing testosterone (6 nmol/L) reflects Australian data from older men (70-89 year old), while noting that it remains as 8.0 nmol/L in consensus guidelines for younger men at this time.

The sponsor looks forward to the further review of testosterone utilisation by DUSC that the PBAC recommended be undertaken twelve months after the implementation of the new PBS restriction.

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.