PUBLIC SUMMARY DOCUMENT
Product: Testosterone, solution for topical administration, 110 mL metered-dose pump, 30 mg per 1.5mL, Axiron®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application
The submission sought an Authority Required listing for androgen deficiency in males who meet certain criteria.

2. Background
This presentation of testosterone had not previously been considered by the PBAC.

3. Registration Status
Testosterone solution was TGA registered on 24 May 2012 for androgen replacement therapy for confirmed testosterone deficiency in males.

4. Listing Requested and PBAC's View
Authority Required (STREAMLINED)

Androgen deficiency in males with established pituitary or testicular disorders;

Androgen deficiency in males 40 years and older who do not have established pituitary or testicular disorders other than ageing, 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 luteinising hormone (greater than 1.5 times the upper limit of the eugonadal reference range for young men);

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

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
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.

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.

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.

The submission proposed that the place in therapy of testosterone topical solution is an alternative therapy to testosterone transdermal gel for androgen deficiency in males.

6. Comparator

The submission nominated testosterone transdermal gel (Testogel®) as the comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented a comparison between testosterone solution and testosterone gel from single-arm studies, based on a single arm open label study of the testosterone solution MTE08 (120 days) and its long term extension MTE09 (180 days) and data from the testosterone gel arms of two randomised double-blind clinical trials (Chiang et al., 2007 comparing testosterone gel with placebo and Swerdloff et al., 2000 comparing the testosterone gel with the testosterone patch).

The following trials had been published at the time of submission:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Testosterone solution		
Single arm open label study		
MTE08/09		
Wang et al.	Efficacy and safety of the 2% formulation of testosterone topical solution applied to the axillae in androgen-deficient men.	Clinical Endocrinology 20 June 2011 [ePub ahead of print]
Testosterone gel		
Single arm of randomised trials (testosterone gel vs patch)		
Chiang et al	Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function.	International Journal of Impotence Research 2007; 19 (4):411-417
Chiang et al.	Testosterone gel monotherapy improves sexual function of hypogonadal men mainly through restoring erection: evaluation by IIEF score.	Urology 2009;73(4):762-766
Swerdloff et al.	Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men.	The Journal of Clinical Endocrinology and Metabolism 2000; 85: 4500-4510.
Wang et al.	Pharmacokinetics of transdermal testosterone gel in hypogonadal men: Application of gel at one site versus four sites: A general clinical research center study.	The Journal of Clinical Endocrinology and Metabolism 2000; 85 (3):964-969.
Wang et al.	Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men.	The Journal of Clinical Endocrinology and Metabolism 2000; 85 (8):2839-2853.
Wang et al.	Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men.	Clinical Endocrinology 2001; 54:739-750.
Wang et al.	Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat Mass, and bone	The Journal of Clinical Endocrinology and Metabolism 2004; 89 (5):2085-2098.

Trial ID/First author	Protocol title/ Publication title	Publication citation
	mineral density in hypogonadal men.	

8. Results of Trials

The primary efficacy outcome reported in the MTE08 study was the proportion of subjects with an average total testosterone level within the normal range (C_{avg} 0-24h: 10.4-36.5 nmol/L). The results are shown in the table below.

Proportion of subjects in MTE08 study with serum C_{avg} (0-24h) total testosterone within normal range (10.4-36.4 nmol/L)

Data set	Baseline n/N (%)(95% CI)	Day 15 n/N (%)(95% CI)	Day 60 n/N (%)(95% CI)	Day 120 n/N (%)(95% CI)
Full analysis set	0/143 (0%)	111/143 (77.6%)	119/143 (83.2%)	116/143 (81.1%)
Completer set	0/138 (0%)	105/138 (76.1%)	117/138 (84.8%)	116/138 (84.1%)

Abbreviations: CI = confidence interval; n = count of events; N = number in group

The primary analysis set for efficacy in the MTE08 study was the 'completer set', which included all subjects who completed the day 120 visit and those who withdrew from the study prior to day 120 due to either an adverse event or lack of efficacy. In the completer set, at all the time points, the lower bound of the 95% CI proportion was > 66.8%; which met the FDA pre-defined statistical requirement.

The majority of patients (77.6%) in the full-analysis set and (76.1%) in the completer set achieved serum total testosterone within the normal range (C_{avg} 0-24h: 10.4-36.5 nmol/L) by Day 15 of treatment; the proportions increased slightly by Days 60 and 120.

The MTE08 trial reported an analysis to determine the effect of antiperspirant/deodorant use on the primary efficacy outcome, as Axiron® is a topical testosterone treatment applied to the underarm. The overall results suggested that the concomitant use of antiperspirant/deodorant did not influence the efficacy of testosterone solution administered to the underarm.

As the proportion of subjects with average total testosterone level within the normal range (C_{avg} 0-24h: 10.4-36.5 nmol/L) was not reported in either the Chiang or Swerdloff studies, the submission also presented two additional co-primary outcomes: mean C_{avg} testosterone (0-24h) and pre-application concentration of total testosterone.

At the end of the studies (Day 120 in the MTE08 study and Day 180 in the Swerdloff study), the serum total testosterone level in the MTE08 study was lower than the testosterone gel in the Swerdloff study.

The mean level of testosterone increased into the normal range (10.4-36.4 nmol/L) at all time points after treatment of testosterone, with changes from baseline comparable between the MTE08/09 study (mean change 9.9 nmol/L) and 50 mg testosterone gel arm in the Swerdloff study (mean change 11.02 nmol/L). A dose concentration effect was demonstrated in the Swerdloff study, with 100 mg doses resulting in higher of serum testosterone concentrations than 50 mg doses.

The pre-application serum testosterone level results suggested that more than 50% of patients treated with either the testosterone gel or the solution had a trough testosterone concentration (pre application), within the normal reference range
(10.4-36.4 nmol/L).

For PBAC's view on these results, see Recommendation and Reasons.

Similar proportions of patients reported adverse events in the MTE08/09, Swerdloff and Chiang studies. There were more reports of application site reactions in MTE08/09, including erythema, irritation, oedema and warmth, while the Swerdloff study only reported mild to intense erythema as adverse events. Differences in reporting of application site reactions may relate to the fact that extension study MTE09 was designed to evaluate skin-safety while Swerdloff only reported the application site effects as adverse events.

9. Clinical Claim

The submission described the testosterone solution as non-inferior in terms of comparative efficacy and safety to testosterone gel. The PBAC accepted this claim based on the data reviewed.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as weighted means of the doses established at steady-state after full titration derived from the MTE08 and Swerdloff studies. The derived equi-effective doses were testosterone solution 69.33 mg and testosterone gel 75.17 mg.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost to the PBS was estimated to be zero over the first 5 years. The submission assumed that testosterone solution will replace only the testosterone gel, in equal quantities.

12. Recommendation and Reasons

The PBAC was of a mind to recommend listing of testosterone solution on the PBS as an Authority Required benefit on a cost minimisation basis compared with testosterone gel. However, in the absence of a decision by the TGA Delegate on the registration of testosterone solution, the PBAC deferred making a final recommendation.

The submission effectively presented a comparison between testosterone solution and testosterone gel across single-arm studies, based on a single arm open label study of the testosterone solution MTE08 (120 days) and its long term extension MTE09 (180 days) and data from the testosterone gel arms of two randomised double-blind clinical trials (Chiang et al., 2007 comparing testosterone gel with placebo and Swerdloff et al., 2000 comparing the testosterone gel with the testosterone patch). The PBAC noted that the majority of patients (77.6%) in the full-analysis set and (76.1%) in the completer set achieved serum total testosterone within the normal range (Cavg 0-24h: 10.4-36.5 nmol/L) by Day 15 of treatment; the proportions increased slightly by Days 60 and 120. In the completer set, at all the time points, the lower bound of the 95% CI proportion was > 66.8%; which met FDA pre-defined statistical requirement.

The PBAC also noted that the mean level of testosterone increased into the normal range (10.4-36.4 nmol/L) at all time points after treatment of testosterone, with changes from baseline comparable between the MET08/09 study (mean change 9.9 nmol/L) and 50 mg testosterone gel arm in the Swerdloff study (mean change 11.02 nmol/L). A dose concentration effect was demonstrated in the Swerdloff study, with 100 mg doses resulting in higher of serum testosterone concentrations than 50 mg doses. The PBAC considered that, as there is normally large variance in individual testosterone concentrations in any untreated population, the interpretation of the clinical importance of small variations in the trial groups is difficult. The PBAC also considered that the interpretation of these results is limited by the lack of a common reference across the studies, the use of different testosterone doses in the trials and differences in baseline testosterone levels in the study populations.

However, the PBAC accepted that testosterone transdermal gel is the appropriate comparator and that testosterone solution is non-inferior overall in terms of comparative effectiveness and safety to testosterone gel.

The PBAC noted that a cost-minimisation analysis was presented in the submission. The equi-effective doses were estimated as weighted means of the doses at steady-state after full titration, derived in the submission from the MTE08 and Swerdloff studies, as being testosterone solution 69.33 mg and testosterone gel 75.17 mg. The PBAC noted that in the Swerdloff study some patients started testosterone at the 100 mg dose rather than the 50 mg dose recommended in the PI and agreed that this method of deriving the equi-effective doses is of questionable validity. The PBAC noted that the submission did not consider the equi-effective doses as a basis to determine the cost even though it is claimed that analysis is based on equi-effective doses.

The submission requested cost-minimisation with testosterone gel 50 mg. The PBAC noted that testosterone solution 60 mg appears to deliver slightly less testosterone than 50 mg testosterone gel with smaller concentration increases reported, albeit with wide confidence intervals. Therefore, on the basis of the clinical data, the PBAC considered that the equi-effective doses to be testosterone solution 70 mg and testosterone gel 50 mg, albeit with some uncertainty.

The PBAC considered that an Authority Required listing for testosterone solution is more appropriate, as a Streamlined Authority is not consistent with the current PBS listings for testosterone products currently listed on the PBS. The PBAC expressed concerns about the potential use of testosterone products in populations in whom the drug has not been evaluated as being cost effective.

The PBAC also recommended that testosterone solution not to be included in the PBS medicines for prescribing by nurse practitioners.

Recommendation:
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13. 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.

14. Sponsor's Comment

The sponsor has no comment.