PUBLIC SUMMARY DOCUMENT
Product: Testosterone undecanoate, injection, 1 g in 4 mL, Reandron®
Sponsor: Schering Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application
To request an authority required listing for use as testosterone replacement in primary and secondary male hypogonadism.

2. Background
This formulation has not previously been considered by the PBAC.

3. Registration Status
Testosterone undecanoate injection was registered by the TGA on 26 October 2005 for testosterone replacement in primary and secondary male hypogonadism.

4. Listing Requested and PBAC's View
Authority required
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 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);
Micropenis, pubertal induction, or constitutional delay of growth or puberty, in males under 18 years of age.

The PBAC accepted the proposed restriction wording. However, the PBAC after noting that the injections would be administered every 10 to 14 weeks, considered that 1 repeat would be more appropriate than the 3 repeats as suggested by the sponsor.

5. Clinical Place for the Proposed Therapy
An alternative product for use as testosterone replacement therapy in primary and secondary male hypogonadism.

6. Comparator
The PBAC accepted the submission's nomination of testosterone implant as the appropriated comparator.

7. Clinical Trials
The basis of the submission, as detailed below, was two non-randomised open-label studies:
- testosterone intramuscular (i.m.) injection 1 g (n=7) over ~33 months
- testosterone implant 1.200 g (n=14; double PBS dose of 600 mg) over 6 months.

Trial/First author	Protocol title	Publication citation
Von Eckardstein et al	Treatment of male hypo-gonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study.	Journal of Andrology 23(3):419-25.
Jockenovel F et al	Pharmacokinetics and pharma-	Clinical Endocrinology 45:61-71.

Trial/First author	Protocol title	Publication citation
	codynamics of subcutaneous testosterone implants in hypogonadal men. .	

8. Results of Trials

In respect to the i.m. injection study, the results showed that as the injection interval was lengthened, testosterone levels decreased, but remained within the reference range (10.4 to 34.7 nmol/L). A 12-weekly dosing interval maintained serum testosterone levels within the required range.

The majority of the adverse events reported with the injection were assessed as not associated with the study drug. Overall, the injection was well tolerated over the trial period of approximately 33 months.

The only side effect observed with the implant was local infection (5.4%), leading to extrusion of 5 pellets in 3 patients (4.5%).

9. Clinical Claim

The PBAC accepted the submission's claim that testosterone i.m. injection was no worse than the testosterone implant (600 mg) in terms of effectiveness, but the "implant was associated with extrusions and infections".

10. Economic Analysis

A preliminary (that is, trial-based) economic evaluation was presented. The PBAC considered the choice of the cost-minimisation approach was valid. The resources included were drug costs, costs of administration and cost of managing side effects.

The submission claimed that the net cost for the injection was lower than that for the implant.

The PBAC considered it appropriate that a modelled economic evaluation was not presented as the submission was based on a cost-minimisation approach.

The equi-effective doses in the context of cost-minimisation were testosterone i.m. injection 1g every 10-14 weeks and testosterone implant (600 mg) every 4-5 months. This relativity was based on results from the two studies that showed that these doses produced serum testosterone concentrations within the reference range (10.4 - 34.7 nmol/L).

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of packs dispensed per year would be less than 5,000 in Year 2 of listing.

The submission estimated that the financial cost per year to the PBS would be well under $1 million in Year 2 of listing. The submission stated that the overall market was expected to grow more rapidly as a result of listing the injection.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis as compared to testosterone implant with a dose relativity of testosterone intramuscular injection 1000 mg every 10 - 14 weeks and testosterone implant (600 mg) every 4 months. The PBAC noted that the cost

minimisation basis of its recommendation is reliant on an average three monthly rate of administration of the injection and requested that the Drug Utilisation Sub-Committee (DUSC) monitor the use of the injection following PBS listing. In the event that PBS usage becomes more frequent, the PBAC may wish to revisit the dose relativities. The PBAC also considered that the dosage requirements of the injection would align with a maximum quantity of one injection with one repeat allowing for 6 months treatment in total which is considered appropriate.

Recommendation:
List

Restriction:	Authority required 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 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); Micropenis, pubertal induction, or constitutional delay of growth or puberty, in males under 18 years of age.
Maximum quantity	1
Repeats:	1

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