PUBLIC SUMMARY DOCUMENT

Product: Triptorelin Embonate, powder for injection and 1 vial solvent 2 mL, 3.75 mg (1 month) and 11.25 mg (3 month) (base), Diphereline®

Sponsor: Ipsen Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission sought an Authority Required PBS listing for locally advanced or metastatic carcinoma of the prostate.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Triptorelin embonate was registered by the TGA on 28 August 2006 for the treatment of locally advanced or metastatic prostate cancer.

4. Listing Requested and PBAC's View

Authority required
Locally advanced (equivalent to Stage C) or metastatic (equivalent to Stage D) carcinoma of the prostate.

The PBAC noted the requested restriction was consistent with those for other medicines currently listed on the PBS for this condition.

5. Clinical Place for the Proposed Therapy

Prostate cancer localised within the prostate gland can be treated successfully with surgery to remove the prostate or radical radiotherapy. However, 30% of those patients will later on develop metastatic disease. Endocrine therapy, which includes the blockade of androgen receptors (anti-androgen therapy) and indirect inhibition of the biosynthesis of androgen (gonadotrophin releasing hormone (GnRH) agonist therapy), is the first and primary means of treatment for patients with metastatic prostate cancer.

Triptorelin is a long acting GnRH agonist, which results in a desensitisation phenomenon by which gonadotrophin secretion is dramatically reduced, resulting in gonadal suppression, in men, and a marked decrease in testosterone production.

6. Comparator

The submission nominated goserelin acetate as the main comparator. The minor comparator was leuprorelin. The PBAC considered both comparators appropriate.

7. Clinical Trials

The submission presented an indirect comparison of triptorelin acetate (three randomised trials) and goserelin acetate (two randomised trials) via the common reference of orchiectomy or pulpectomy (partial orchiectomy for cosmetic reasons).

These trials had been published at the time of submission, as follows:

Triptorelin versus orchidectomy

Trial/First author	Protocol title	Publication citation
Ipsen Clinical Study 914 CL 17E Botto H et al	Decapeptyl in the treatment of advanced prostatic cancer: comparative study with pulpectomy	Therap Progress in Urological Cancers 1989 pages 53-60
Ipsen Clinical Study 914 CL 7P De Sy WA et al	Long term experience in the treatment of advanced prostate cancer with decapeptyl, in comparison to orchiectomy	Acta Urologica Belgica 1988 56(4) 581-588
Ipsen Clinical Study 914 CL 14P Parmar H et al	Orchiectomy versus long-acting D-TRP-6-LHRH in advanced prostate cancer	Brit J Urology 1987 59: 248-254
Parmar et al	Medical or surgical orchiectomy? 6 year survival outcomes from Study 914CL 14.	Brit Med J 1991, 302:1272

Goserelin versus orchidectomy

Trial/First author	Protocol title	Publication citation
Kaisary AV et al	Comparison of LHRH analogue (Zoladex) with orchiectomy in patients with metastatic prostatic cancer	Brit J Urology 1991 67: 502-508
Vogelzang NJ et al	Goserelin versus orchiectomy in the treatment of advanced prostate cancer: Final results of a randomised trial	Urology 1995 46: 220-226

Triptorelin embonate versus leuprorelin acetate

Trial/First author	Protocol title	Publication citation
Ipsen study DEB 96-TRI-01 (Phase II) Heyns CF et al	Comparative efficacy of triptorelin embonate and leuprorelin acetate in men with advanced prostate cancer	BJU International 2003 92: 226-231

8. Results of Trials

Trial data for death and overall survival time were measured in weeks from therapy initiation to patient's death, regardless of additional therapeutic measures taken during or after the 2-year treatment period. Both the fixed and random effects pooled absolute risk and relative risk estimates identified no statistically significant difference between goserelin, triptorelin and orchiectomy in terms of mortality.

A reanalysis conducted during the evaluation of the submission to estimate the indirect comparison of triptorelin versus goserelin found that there was no difference in the relative risk of death between goserelin and triptorelin.

Pharmacodynamic and pharmacokinetic studies provided in the submission were evaluated for absorption and testosterone level control. Despite inadequate information in some of the studies to assess baseline comparability and significant differences in the extent and rate of absorption between the two formulations (embonate and acetate), they were equivalent in terms of pharmacodynamics as assessed by testosterone serum levels. There was no evidence of an accumulative effect.

In the trials, the most commonly reported adverse events were hot flushes, bone pain, headache and musculoskeletal pain. Toxicity and adverse events seem to be comparable between triptorelin and goserelin.

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

9. Clinical Claim

The submission described triptorelin as having equal effectiveness and toxicity with goserelin and other GnRH agonists.

This description was considered by the PBAC to be reasonable, based on the supporting data.

10. Economic Analysis

The submission presented a preliminary economic evaluation using a cost-minimisation approach. The resources included were drug costs.

A modelled economic evaluation was not presented.

The equi-effective doses in the context of cost-minimisation were triptorelin embonate 3.75 mg once monthly, for duration as necessary, and goserelin acetate 3.6 mg once monthly for duration as necessary.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 2 of listing the likely number of packs dispensed would be < 10,000 prescriptions for both formulations and the financial cost to the PBS would be < $10 million.

12. Recommendation and Reasons

The PBAC recommended listing on a cost minimisation basis with goserelin acetate with the equi-effective doses being triptorelin embonate (Diphereline®) 3.75mg once monthly, for duration as necessary, and goserelin acetate (Zoladex®) 3.6mg once monthly for duration as necessary; and triptorelin embonate (Diphereline®), 11.25mg once every three months, for duration as necessary, and goserelin acetate (Zoladex®), 10.8mg once every three months for duration as necessary. The equi-effective doses are based on the key trials of triptorelin and

goserelin versus orchiectomy as the common reference, and pharmacodynamic studies showing equivalence in terms of serum concentrations of testosterone between triptorelin acetate and triptorelin embonate for which listing is proposed.

The PBAC noted that the submission based its claim of non-inferiority with goserelin acetate on a series of clinical trials dating from the late 1980s and early 1990s and that these trials were conducted with less rigour than is the case currently. However the Committee was satisfied that non-inferiority had been established. The PBAC further noted that triptorelin embonate and goserelin acetate belong to the same pharmacological group of gonadotropin releasing hormone agonists and this gives extra support for a cost-minimisation listing.

The PBAC recommended the 20 day safety net rule should apply.

Recommendation

Triptorelin Embonate, powder for injection and 1 vial solvent 2mL, 3.75 mg (1 month) and 11.25 mg (3 month) (base)

Restriction:	Authority required Locally advanced (equivalent to Stage C) or metastatic (equivalent to Stage D) carcinoma of the prostate.
Maximum quantity:	1
Repeats:	5 (3.75 mg) and 1 (11.25 mg)

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.