PUBLIC SUMMARY DOCUMENT

Product: Letrozole, tablet 2.5 mg, Femara®

Sponsor: Novartis Pharmaceuticals Australia Pty Limited

Date of PBAC Consideration: March 2007

1. Purpose of Application

The resubmission requested a change to the current PBS listing of letrozole to permit its use by women who have received standard adjuvant therapy with tamoxifen citrate. The use of letrozole in this setting is known as "extended adjuvant".

2. Background

Letrozole was listed on 1 May 1998 on a cost-minimisation basis compared to anastrozole, with letrozole 2.5 mg/day being considered to be equivalent to anastrozole 1 mg/day for the treatment of advanced breast cancer in post-menopausal women with disease progression following treatment with tamoxifen citrate.

At the March 2002 meeting, the PBAC recommended first-line use in this patient group. At the March 2005 meeting, the PBAC deferred a submission to extend the restricted benefit listing of letrozole to include treatment of early-stage hormone-dependent breast cancer in post-menopausal women who have completed standard adjuvant therapy with tamoxifen. The PBAC sought clarification of the incremental cost-effectiveness ratios based on distant recurrence alone, ie excluding local recurrence. The November 2005 resubmission was rejected on the grounds that the revised base case modelled incremental discounted extra QALY gained for distant metastases only was considered unacceptably high.

A submission to the July 2006 PBAC seeking to include treatment of hormone-dependent early breast cancer also included updated cost-effectiveness ratios in the extended adjuvant setting. The PBAC recommended that letrozole should be PBS listed for use in early breast cancer and that the total duration of PBS-subsidised adjuvant hormonal treatment (tamoxifen + aromatase inhibitors) should not exceed 5 years. Thus, the application for use of letrozole in the extended adjuvant setting was rejected by the PBAC.

The Public Summary Document for the July 2006 submission can be found at: www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-letrozole-july06.

3. Registration Status

As at 16 April 2007 the letrozole (Femara®) indication recorded in the Australian Register of Therapeutic Goods (ARTG) is: 'treatment of postmenopausal women with hormone receptor positive breast cancer'.

4. Listing Requested and PBAC's View

Restricted benefit
Treatment of hormone-dependent breast cancer in post-menopausal women.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Letrozole will provide a treatment in the extended adjuvant setting of hormone-dependent breast cancer in post menopausal women.

6. Comparator

The submission nominated placebo (no extension of hormonal intervention) as the comparator.

7. Clinical Trials

The resubmission relied on the same head-to-head trial comparing letrozole 2.5mg and placebo in a total of 5,170 subjects over 5 years as did the previous submissions. After the first interim analysis (28 months), the difference in disease recurrence favoured the letrozole group and crossed the pre-specified boundaries for unblinding the study, so patients and investigators were unblinded and patients in the placebo group were given the opportunity to cross-over to letrozole treatment. In effect, 50% of patients completed ≥2 years, 24% completed ≥3 years, and 10% completed ≥4 years of the trial. No changes had been made to the trial data presented in the previous re-submissions.

Since the last resubmission the following papers and economic evaluations have been published:

Trial/First author	Protocol title/Publication title	Publication citation
Goss PE et al, 2005	Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.	Journal of the National Cancer Institute 2005; 97:1262-1271
Perez EA et al, 2006	Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17.	Journal of Clinical Oncology 2006; 24:3629-3635
Wasan KM et al, 2005	The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA.17L).	Annals of Oncology 2005; 16:707-715
Delea TE et al, 2006	Cost-effectiveness of extended adjuvant letrozole therapy after 5 years of adjuvant tamoxifen therapy in postmenopausal women with early-stage breast cancer.	American Journal of Managed Care 2006; 12:374-386
Karnon J et al, 2006	Cost effectiveness of extended adjuvant letrozole in postmenopausal women after adjuvant tamoxifen therapy: the UK perspective.	Pharmacoeconomics 2006; 24:237-250

8. Results of Trials

The key results are summarised in the table below:

Results at median 28 months of follow-up	Letrozole (N=2,582)	Placebo (N=2,586)
Patients with recurrence events, n (%)	92 (3.6)	155 (6.0)
Hazard ratio of recurrence events (95% CI)	0.58 (0.45, 0.76), p=0.00003	
Overall survival year 4	2.0%	2.4%
Hazard ratio overall survival year 4 (95% CI)	0.82 (0.57, 1.19)	
Hazard ratio overall survival, node positive	0.61 (0.38, 0.97)	
Contralateral breast cancer (CBLC) as first event, n (%)	19 (0.7)	29 (1.1)
Recurrences excluding CLBC, n (%)	73 (2.8)*	126 (4.9)
Local breast recurrence	9*	22
Local chest wall recurrence	2	8
Regional recurrence	7	4
Distant recurrence†	55*	92

[a] *n is 2,575 for letrozole, and 2582 for placebo*

† First observation of distant metastases may involve multiple sites * p<0.05

The number of patients with recurrence events was significantly lower in the letrozole group than in the placebo group. Local breast recurrence and distant recurrence, especially bone metastases, were also significantly lower in the letrozole group.

At the time of the main analysis, there was no difference in overall survival between patients in the letrozole and placebo groups (51 deaths in the letrozole group and 62 in the placebo group, HR=0.82; 95% CI: 0.56, 1.19). Analysis of overall survival by the stratification factors showed that the majority of deaths were in women who had node positive disease (28 deaths in the letrozole group and 45 in the placebo group). A statistically significant difference in survival was observed for these patients (HR=0.61; 95% CI: 0.38, 0.97). At the time of the updated safety analysis, the difference was no longer significant, as over half of the placebo group patients crossed over to the letrozole group following the un-blinding of the results.

No new toxicity data was presented in the re-submission. The occurrences of serious adverse events were similar across both arms (14 in the letrozole and 13 in the placebo group). The number of total deaths was numerically lower in the letrozole group (51 vs. 62). There was a higher incidence of new cases of osteoporosis in patients in the letrozole group. The incidence of bone fractures for letrozole patients was not significantly higher at the time of analysis. The clinical relevance and effects of the higher incidence of osteoporosis and any associated effects and costs remained unclear. There was no statistically significant difference in fracture incidence between the letrozole and placebo groups.

9. Clinical Claim

The submission claimed that letrozole is more effective than placebo, but more toxic. The PBAC accepted, on the evidence presented, that the claim was reasonable.

10. Economic Analysis

An updated preliminary economic evaluation was presented, using the lower cost of letrozole. All other variables and assumptions remained the same. The trial-based incremental discounted cost per extra discounted additional disease-free month was calculated to be < $10,000.

An updated modelled economic evaluation was also presented.

The base case modelled incremental discounted cost per discounted QALY was calculated to be in the range of $30,000- 35,000, The base case modelled cost effectiveness based on distant metastases only (calculated during the evaluation) was in the range $40,000 to $45,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year estimated to on letrozole was < 5 000, while the financial cost per year to the PBS was estimated to be < $5 million per year in Year 1 – 4.

12. Recommendation and Reasons

The PBAC recommended the listing of letrozole for extended adjuvant treatment of early breast cancer after treatment with tamoxifen on the basis of high but acceptable cost-effectiveness compared to placebo (no extension of hormonal treatment). The total duration of treatment in early breast cancer with letrozole (or any other aromatase inhibitor) should not exceed 5 years, and treatment in the extended adjuvant setting should commence within 6 months of ceasing tamoxifen.

The PBAC noted that the National Breast Cancer treatment guidelines recommended the use of letrozole in the extended adjuvant setting for women at high risk of disease recurrence (defined by node positive disease and/or tumour size> 20 mm and/or Grade 2-3 tumours). However, the Committee considered the evidence presented provided an insufficient basis to restrict the use of letrozole to this patient group.

The PBAC agreed with the sponsor's proposal that allowing treatment with letrozole in the extended adjuvant setting to commence up to six months after ceasing tamoxifen would permit sufficient time for patients to consult with a medical oncologist after ceasing tamoxifen.

The PBAC considered the matter of whether women were at increased risk of experiencing distant metastases after experiencing a contralateral or loco-regional recurrence was not known and did not accept the submission's cost per QALY associated with distant metastases alone. However, it agreed that the cost/QALY calculated during evaluation was high but acceptable.

Recommendation
Letrozole, tablet, 2.5 mg

Amend the restriction to read:

> Restricted benefit
> Treatment of hormone-dependent advanced breast cancer in post-menopausal women;
> Treatment of hormone-dependent early breast cancer in post-menopausal women;
> Extended adjuvant treatment of hormone-dependent early breast cancer in post-menopausal women commencing within 6 months of ceasing treatment with

tamoxifen citrate.

NOTE:
This drug is not PBS-subsidised for primary prevention of breast cancer.
This drug is not PBS-subsidised for adjuvant hormonal treatment of early breast cancer extended beyond 5 years.
This drug is not PBS-subsidised for extended adjuvant early breast cancer treatment where the total duration of letrozole treatment extends beyond 5 years.

Maximum quantity: 30
Number of repeats: 5

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

Novartis Pharmaceuticals Australia thank the PBAC for recommending the use of letrozole in the extended adjuvant setting of early breast cancer.