PUBLIC SUMMARY DOCUMENT

Product: Letrozole, tablet, 2.5 mg, Femara®

Sponsor: Novartis Pharmaceuticals Australia Pty Limited

Date of PBAC Consideration: July 2006

1. Purpose of Application

To extend the current restricted benefit listing for letrozole to include the treatment of hormone-dependent early breast cancer in post-menopausal women, and for use in the extended adjuvant setting.

2. Background

Letrozole was listed on 1 May 1998 on a cost-minimisation basis compared to anastrozole, with 2.5 mg letrozole daily being considered to be equivalent to 1 mg anastrozole daily 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 considered a third submission to allow first-line use in patients with advanced disease. The PBAC recommended the listing be amended on the basis of acceptable cost-effectiveness in the context of a trend to improved survival and an improved quality of life achieved with letrozole, compared with tamoxifen, associated with clear evidence of a delay in the time to disease progression.

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 (known as the extended adjuvant setting). 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 the revised base case modelled incremental discounted extra QALY gained of less than $60,000 for distant metastases only was considered unacceptably high.

The July 2006 submission included updated cost-effectiveness ratios in the extended adjuvant setting and presented new data in the early adjuvant setting.

3. Registration Status:

In April 2006 the TGA expanded the registration of letrozole to the treatment of post-menopausal 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.
NOTE:
This drug is not PBS-subsidised for primary prevention of breast cancer.

The PBAC considered the total duration of PBS-subsidised adjuvant hormonal treatment (tamoxifen and aromatase inhibitors) should not exceed five years.

5. Clinical place for the proposed therapy

Letrozole will provide an alternative treatment to tamoxifen and anastrozole in the treatment of early breast cancer in post-menopausal women.

6. Comparator

The submission appropriately nominated anastrozole as the comparator for adjuvant treatment in the early breast cancer setting.

7. Clinical Trials

The submission presents an indirect comparison of two randomised trials in post-menopausal women with early breast cancer comparing letrozole 2.5 mg/day with tamoxifen 20 mg/day (BIG1-98) and anastrozole 1 mg/day with tamoxifen 20 mg/day (ATAC – first analysis with a duration of 33.3 months).

The trials were published at the time of the submission as follows.

Trial/First author	Publication title	Publication citation
BIG 1-98 Collaborative Group - Thuerlimann B,	A comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer	N Eng J Med 2005; 353 (26) 2747-57
The ATAC Trialists' Group – M Baum	Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial	The Lancet 2002; 359:2131-39

The clinical trial evidence for the extended adjuvant setting was not represented in the submission before the PBAC in July 2006. These data can be found in the Public Summary Documents following the November 2005 PBAC meeting.

8. Results of Trials

In the adjuvant treatment of early breast cancer, the event rates for tamoxifen were similar across the letrozole versus tamoxifen and anastrozole versus tamoxifen trials. Both letrozole and anastrozole resulted in a statistically significant increase in disease free survival compared with tamoxifen. The hazard ratio was 0.81 (0.70, 0.93) for letrozole vs tamoxifen and 0.83 (0.71, 0.96) for anastrozole vs tamoxifen. The differences in the proportion of women who remained disease free at five years were 2.6% for letrozole and 2.8% for anastrozole versus tamoxifen. The submission did not provide any Kaplan-Meier curves for the outcomes in each trial.

The analysis of DFS in which second primary malignancies are excluded is the same definition of DFS used in the ATAC study. The hazard ratio of 0.79 (0.68, 0.92) for

letrozole vs tamoxifen is similar to the ATAC hazard ratio of 0.83 (0.71, 0.96) for anastrozole vs tamoxifen.

In positive-hormone receptor patients, both letrozole and anastrozole resulted in a statistically significant increase in disease free survival compared with tamoxifen.

Overall, the incidence of AEs in the two trials was similar. Treatment with either letrozole or anastrozole resulted in a statistically significantly higher incidence of fractures compared with tamoxifen. Letrozole resulted in significantly more arthralgia/arthritis and osteoporosis, and anastrozole resulted in significantly more musculoskeletal disorders than tamoxifen. In both trials, the use of tamoxifen was associated with a statistically significantly higher incidence of hot flashes/flushes, vaginal bleeding and thromboembolic events.

9. Clinical Claim

The submission claimed that letrozole was no worse than anastrozole in terms of effectiveness and toxicity in the early breast-cancer setting. The PBAC accepted that, based on the supporting data, this description was reasonable.

The equi-effective doses in the context of cost-minimisation were letrozole 2.5mg and anastrozole 1mg. These are based on the doses used in the BIG and ATAC trials.

10. Economic Analysis

A preliminary economic evaluation in the adjuvant setting was not necessary as the submission was based on cost-minimisation.

A modelled economic evaluation in the adjuvant setting was also not necessary.

The submission provided an updated cost-effectiveness analysis for the use of letrozole in the extended adjuvant setting. The estimated cost-effectiveness ratios for letrozole in the extended adjuvant setting were in the range of $15,000 - $45,000 per life year gained and per QALY gained in the base case, and less than $55,000 per QALY in the avoidance of distant recurrence. The submission asserted that letrozole is a cost-effective intervention for the extended adjuvant treatment of women with early-stage breast cancer.

11. Estimated PBS Usage and Financial Implications:

The submission estimated the likely number of packs dispensed per year to be less than 120 000 in Year 4 for both the early breast cancer setting and the extended adjuvant setting.

The submission estimates the financial cost per year to the PBS of < $10 million in Year 4 (cost-offsets for drugs in the early setting only, not the extended setting). The overall market was not expected to grow or to grow more rapidly as a result of listing letrozole in the early breast cancer setting.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis with anastrozole in the early breast cancer setting. The equi-effective doses are letrozole 2.5 mg and anastrozole 1 mg. The total duration of PBS-subsidised adjuvant hormonal treatment (tamoxifen + aromatase inhibitors) should not exceed 5 years. The PBAC requested that the PBPA negotiate a risk sharing agreement with the sponsor.

The PBAC did not agree that letrozole should be PBS-subsidised for use in the extended adjuvant setting. The Committee considered that grounds upon which it had previously rejected use in this setting remained largely unresolved and that the revised incremental cost effectiveness ratio per quality adjusted life year (QALY) of less than $55,000, remained unacceptable. This was only slightly decreased from that before the PBAC in November 2005 because the price of letrozole had fallen to match that of anastrozole. The PBAC recalled it had uncertainty about this estimate because no overall survival gain was demonstrated in the MA17 trial; no adverse impact of letrozole on mortality or health care resources was included in the economic model and that the clinical course of people who relapse after prophylactic exposure to letrozole in the economic model is no different to the natural history of those who had never received letrozole.

Recommendation
Amend the current listing to read:

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

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 is pleased that Femara (letrozole) will be PBS listed for adjuvant treatment of early breast cancer and thanks the PBAC for this recommendation.

Novartis also provided evidence in the submission to support the cost-effectiveness of letrozole in the extended adjuvant setting. Letrozole is the only endocrine therapy shown to significantly reduce the risk of further disease recurrence in women who have completed adjuvant tamoxifen therapy. Novartis is committed to helping women with breast cancer gain access to treatment and will continue to pursue reimbursement in the extended adjuvant setting.