PUBLIC SUMMARY DOCUMENT
Product: LETROZOLE, tablet, 2.5 mg, Femara®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

To extend the restricted benefit listing for letrozole to include the treatment of early-stage hormone-dependent breast cancer in post-menopausal women who have completed no less than 4.5 years of standard adjuvant tamoxifen therapy.

2. Background

Letrozole was listed on 1 May 1998 on a cost-minimisation basis compared to anastrozole 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 re-submission to allow first-line use for advanced breast cancer in hormone receptor positive post-menopausal women. 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. The PBAC sought clarification of the incremental cost-effectiveness ratios based on distant recurrence alone, ie excluding local recurrence.

3. Registration Status

Letrozole is TGA registered for:

- Extended adjuvant treatment of early breast cancer in post-menopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment of advanced breast cancer in post-menopausal women.
- Treatment of advanced breast cancer in post-menopausal women after relapse or disease progression following antioestrogen (eg tamoxifen) therapy.

For all indications, efficacy has not been demonstrated in patients with hormone receptor negative disease.

4. Listing Requested and PBAC's View

Restricted benefit

Treatment of early-stage hormone-dependent breast cancer in post-menopausal women who have completed no less than 4.5 years of standard adjuvant tamoxifen therapy.

NOTE:

This drug is not PBS-subsidised for primary prevention of breast cancer.
Patients entering the study for letrozole for early-stage breast cancer following standard tamoxifen therapy were to be within three months of completing their tamoxifen therapy.

The PBAC did not comment on the wording of the requested listing.

5. Clinical Place for the Proposed Therapy

Under current treatment practices, post menopausal women with early-stage breast cancer receive five years only of tamoxifen therapy (with or without chemotherapy) following surgery as evidence suggests that there is no benefit from continuing tamoxifen treatment beyond five years. There is currently no endocrine therapy used in those women to prevent disease recurrence once they have completed standard tamoxifen therapy. The submission sought to list letrozole in this 'extended' adjuvant setting.

6. Comparator

The PBAC accepted the submission's nomination of placebo as the main comparator.

7. Clinical Trials

The submission presented a single head-to-head randomised, double-blind, parallel-group, multi-centre trial comparing letrozole 2.5mg and placebo in a total of 5,170 subjects. Eligible patients were randomised to receive either intervention once daily for a period of 5 years, with trial subjects followed up for life. Most subjects (98%) were receptor-positive and 46% had a positive nodal status. The first interim analysis occurred after a median duration of follow up of 2.4 years (28 months). Because the difference in disease recurrence was more favourable in the letrozole group and crossed the pre-specified boundaries for study unblinding, 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.

Trial/First author	Protocol title	Publication citation
Goss P	A randomised trial of letrozole in post-menopausal women after five years of tamoxifen therapy for early stage breast cancer	NEJM 2003; 349(19):1-10

8. Results of Trials

After a median follow-up of 28 months, the hazard ratio for a recurrence event for letrozole vs placebo was 0.58 (95% CI: 0.45 to 0.76), a 42% risk reduction. Based on the difference in time to first recurrence, the estimated 4-year disease-free survival (DFS) was 93% for letrozole and 87% for placebo ($p<0.001$). There was no significant difference observed in overall survival between the total letrozole and placebo groups at the time of analysis (51 and 62 deaths, respectively), but there was a significant improvement in overall survival for women with node positive disease (HR for death of 0.61 for letrozole vs placebo, $p=0.035$), and the occurrence of distant metastases was significantly lower in letrozole group (55 vs 92, $p<0.003$).

The occurrences of serious adverse events were similar across the 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. Although the incidence of bone fractures for letrozole patients was not significantly higher at the time of analysis, given the numerical difference, and the experience with anastrozole in the ATAC trial, the PBAC considered this trend may become more pronounced with a larger number of patients treated for a longer time.

9. Clinical Claim

The submission claimed that letrozole is more effective than placebo, but more toxic.

For PBAC's view see the Recommendation and Reasons.

10. Economic Analysis

The submission did not present a preliminary economic evaluation and this was considered appropriate by the PBAC as there were no changes to the drug price or the restriction and no new data.

The submission presented an updated modelled economic evaluation. The updated evaluation calculated the incremental cost-effectiveness ratios based on distant recurrence alone, with the exclusion of local recurrence.

The base case modelled incremental discounted cost/extra discounted outcome was $15,000 - $ 45,000 per LYG or QALY gained based on all recurrence. When the analysis was restricted to consider only the reduction in distant recurrence (as requested by the PBAC) the resulting ratios were $45,000 - $75,000 per extra LYG and per extra QALY gained.

For PBAC's view see the Recommendation and Reasons

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients per year to be up to 10,000 in Year 4 of listing.

The financial cost per year to the PBS was estimated to be up to $10-30 million in Year 4.

12. Recommendation and Reasons

The PBAC noted that the number of individuals needed to treat to prevent a recurrence is high. There were 2.4% fewer relapses or new cancers in the letrozole group at 2.4 years ie treatment for 41 women for 2.4 years to prevent one cancer recurrence (100 women for 1 year). For prevention of distant recurrences, 66 women (1.5% absolute risk difference) would need to be treated for 2.4 years (158 women for one year) to prevent one distant recurrence. Although the PBAC considered that prevention of recurrence is important, it is likely that the magnitude of the difference between placebo and letrozole will decline if long term follow-up were to be undertaken (ie beyond 2.4 years). Early changes in disease free survival often do not translate into improvements in overall survival (and even where this occurs the magnitude of the effect is attenuated). The PBAC noted that allowing the study to mature would have addressed the question of survival. The long-term risks and benefits of this therapy in the extended adjuvant setting thus remain unknown.

The PBAC noted that there was no change in overall survival or any improvement in quality of life. A statistically significant decline in the domains of physical functioning, bodily pain, vitality, vasomotor and sexual domains was observed in the letrozole group (J Clinical Oncology; October 2005). The adverse event rate of treatment would be 5.5% more cases of arthralgia/arthritis (one case every 18 women treated over 2.4 years), 1.4% more osteoporosis (one case every 71 women treated). It was also noted that the difference between bone fractures has increased with the 2.5 month update (0.4% now 0.8%) but remained non-significant (p=0.302).

The PBAC did not accept a number of assumptions made in the economic model regarding persistence of treatment effect, survival difference, the impact of adverse events and the clinical course of treatment for patients with disease recurrence.

However, even the base-case modelled incremental discounted cost per extra discounted extra QALY gained was considered unacceptably high.

The PBAC therefore rejected the submission because of an unacceptably high cost-effectiveness ratio.

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 is committed to securing a PBS listing for Femara for the treatment of Australian women with early-stage hormone-dependent breast cancer who have completed standard tamoxifen therapy. Since the decision by the PBAC in November 2005, Novartis Pharmaceuticals has met with representatives from the PBAC and the Department of Health and Ageing and is currently assessing all its options with respect to pursuing a listing that will allow such women access to PBS subsidised Femara.

In the meantime, Novartis Pharmaceuticals suggests that post-menopausal women with hormone-dependent early-stage breast cancer who are about to, or have recently completed their standard adjuvant tamoxifen therapy speak to their physician about future treatment options.