

PUBLIC SUMMARY DOCUMENT

Product: Exemestane, tablet, 25 mg, Aromasin[®]

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

To extend the current restricted benefit PBS listing for exemestane to include the treatment of early breast cancer following 2 years of tamoxifen therapy.

2. Background

At the December 2000 meeting, the PBAC recommended listing exemestane as a restricted benefit for the treatment of oestrogen-receptor positive advanced breast cancer in post-menopausal women with disease progression following treatment with tamoxifen citrate on a cost-minimisation basis with 25 mg exemestane daily equivalent to 1 mg anastrozole daily and 2.5 mg letrozole daily.

3. Registration Status

Exemestane was registered on 9 October 2000 for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.

Exemestane was registered on 27 April 2006 for the sequential adjuvant treatment of oestrogen receptor-positive early breast cancer in post-menopausal women who have received prior adjuvant tamoxifen therapy.

4. Requested Listing and PBAC View

Restricted benefit

Treatment of hormone-dependent early breast cancer in post-menopausal women following a minimum of 2 years treatment with tamoxifen citrate.

The PBAC recommended that the total duration of PBS-subsidised adjuvant hormonal treatment (tamoxifen + aromatase inhibitors) should not exceed 5 years.

5. Clinical place for the proposed therapy

Exemestane may be used as an alternative to tamoxifen in the treatment of early breast cancer in post-menopausal women after patients have been treated with tamoxifen for 2 years or more. Exemestane is also used in advanced breast cancer.

6. Comparator

The submission appropriately nominated tamoxifen as the main comparator, and anastrozole as a secondary comparator.

7. Clinical Trials

The submission presented studies of treatments after at least 2 years of tamoxifen treatment:

Exemestane vs tamoxifen: a single randomised trial (031) of post-menopausal women who had received tamoxifen (20/30mg/day) for 2-3 yrs were then randomized to either exemestane (25mg/day; N=2352) or continued tamoxifen (20/30mg/day, N=2372); follow-up of 2-3 years (mean 27 months). The primary outcome was disease free survival (time from randomisation to recurrence of breast cancer, diagnosis of 2^o breast cancer or death from any cause)

Exemestane vs anastrozole: indirect comparison of two 'sets' of trials comparing exemestane (25mg/day) vs tamoxifen (20/30mg/day) and anastrozole (1mg/day) vs tamoxifen (20/30mg/day) in early breast cancer

- i) exemestane vs tamoxifen: Study 031 (see above)
- ii) anastrozole vs tamoxifen: two studies.

The trials published at the time of the submission were:

Trial/First author	Publication title	Publication citation
Study 031/ Coombs, R et al	A randomised trial of exemestane after 2-3 years of tamoxifen therapy in postmenopausal women with primary breast cancer.	NEJM 2004;350 (11): 1081-92
Jakesz, R et al	Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen:combined result of ABCSG trial 8 and ARNO 95 trial.	Lancet, 2005 (9484) 455-62.
Boccardo, F et al.	Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary result of the Italian Tamoxifen Anastrozole Trial.	J. of Clinical Oncology, 2005, 23 (22) 5138-47.

8. Result of Trials

1. Exemestane vs tamoxifen

There was a statistically significant difference in disease free survival favouring exemestane in the primary analysis, but there was no difference in overall survival.

Disease free survival (primary) and secondary outcomes

Outcomes	Kaplan Meier probability at 3 years >randomisation		Hazard Ratio (95% CI)
	Exemestane (N=2352)	Tamoxifen (N=2372)	
Primary outcome Disease free survival^a	90%	86%	0.69 (0.58-0.82)^a
Adjusted ^b			0.66 (0.55, 0.79)
Secondary outcomes			
Breast cancer free survival	92%	88%	0.65 (0.54-0.79)
Contralateral breast cancer survival	99%	99%	0.32 (0.15-0.72)
Distant recurrence free survival	93%	91%	0.70 (0.56-0.86)
Overall survival	95%	94%	NS

a: number of patients at risk = 4724

b: adjusted for pre-specified prognostic factors: ER status, lymph node status, previous chemotherapy, previous HRT, and bisphosphonate therapy. There was no significant difference in the proportion of women taking bisphosphonate: 1.8% in the exemestane arm and 1.4% in the tamoxifen arm.

2. Exemestane vs anastrozole

The event rates for tamoxifen were similar across the exemestane versus tamoxifen and the anastrozole versus tamoxifen trials. Both exemestane and anastrozole resulted in a statistically significant increase in disease free or event free survival compared with tamoxifen. There was no statistically significant difference in overall survival between treatments.

Distant recurrence free survival was significantly increased for exemestane (031) and anastrozole vs tamoxifen (Jakesz). Contralateral breast cancer free survival was significantly increased only for exemestane vs tamoxifen.

In the summary of the indirect comparison using meta-analysis, there were no statistically significant differences between exemestane and anastrozole, using tamoxifen as the common comparator, for any of the outcomes. Testing assumptions in sensitivity analyses did not change the results.

The Boccardo study, which assessed anastrozole and tamoxifen, was not included in the main analysis as the patient population was deemed to be different in terms of disease severity. In order to assess the robustness of the results from the main analysis, the analyses were re-run including Boccardo data in the anastrozole comparison. Including Boccardo did not alter the conclusions from the main analyses.

There were significantly more adverse events in exemestane-treated patients than in tamoxifen-treated patients. The most common all causality treatment-emergent illnesses or events occurring with an incidence of $\geq 5\%$ in patients in either treatment group or achieving statistical significance at 1% level included arthralgia, insomnia, cardiovascular disorder, osteoarthritis and osteoporosis. Adverse events more common with tamoxifen treatment included thromboembolism, endometrial hyperplasia and uterine polyp.

In the Jakesz study there were significantly more fractures and fewer thromboses in patients treated with anastrozole compared with tamoxifen. In contrast, there were no statistically significant differences between exemestane and tamoxifen in terms of fractures, but the exemestane trial, via an amendment to the original trial protocol, allowed the prophylactic use of bisphosphonates with exemestane.

9. Clinical Claim

The submission claimed:

- 1) exemestane has significant advantages in effectiveness over tamoxifen and having similar or less toxicity; and
- 2) exemestane was no worse than anastrozole in terms of effectiveness and toxicity.

The PBAC accepted that exemestane has advantages in the adjuvant treatment setting for those already taking tamoxifen. The Committee however noted that the follow-up in the trial 031 is short, and that a consequence of this was that the reported hazard ratio for

overall survival of 0.69 (95% CI 0.58 – 0.82) was probably an overestimate. The Committee further noted that exemestane has a different toxicity profile to tamoxifen. The equi-effective dose in the context of cost minimisation was exemestane 25 mg /day equivalent to anastrozole 1 mg/day.

10. Economic Analysis

In the comparison of exemestane vs tamoxifen, a preliminary economic evaluation is presented. The choice of the cost-effectiveness approach was valid.

The trial-based incremental cost per extra disease free year was estimated to be < \$15,000. The trial-based incremental cost per contralateral breast cancer prevented was estimated to be > \$200,000.

A modelled economic evaluation was presented. The choice of the cost-utility approach was valid. The type of model used was a Markov model, constructed using Excel software. The model has two treatment arms: exemestane and tamoxifen. The model has a 38-year duration (starting age of 63), with a 6 monthly cycle length. The model discounts both costs and health benefits at 5% per annum. Half cycle corrections are incorporated into the model. The utilities were from the Harvard List of Preference scores and did not include any decreased utility component for adverse events. The resources included were drug costs, and health care costs (breast cancer recurrence, palliative care and adverse events).

The base case modelled incremental discounted cost per extra discounted QALY is estimated to be in the range of \$15,000 - \$45,000. The base case modelled incremental discounted cost per extra discounted life year is estimated to be in the range of \$15,000 - \$45,000. The base case modelled incremental discounted cost per extra discounted disease free year is estimated to be in the range of \$15,000 - \$45,000.

11. Estimated PBS Usage and Financial Implications

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

The financial cost/year to the PBS was estimated to be < \$10 million in Year 4. The overall market was not expected to grow or to grow more rapidly as a result of listing exemestane.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-effectiveness basis against tamoxifen for the adjuvant hormonal treatment of early breast cancer. The total duration of PBS-subsidised adjuvant hormonal treatment (tamoxifen + aromatase inhibitors) should not exceed 5 years.

The PBAC accepted that exemestane has advantages in the adjuvant treatment setting for those already taking tamoxifen. The Committee however noted that the follow-up in the trial is short, and that a consequence of this was that the reported hazard ratio for overall survival of 0.69 (95%CI 0.58 – 0.82) was probably an overestimate. The Committee

further noted that exemestane has a different toxicity profile to tamoxifen. The modelled cost-effectiveness ratios presented in the submission were considered acceptable by the Committee.

The Committee considered that a question which was not addressed by the submission was whether adjuvant hormonal treatment with tamoxifen for 2 years followed by exemestane for 3 years is equivalent to 5 years of adjuvant treatment with an aromatase inhibitor. If this is the case, then 5 years of aromatase inhibitor treatment should be cost-minimised against this. The Committee noted that the BIG study will answer this question, and requested that the sponsor provide the results from this study as soon as they become available.

The PBAC requested that the PBPA negotiate a risk sharing agreement with the sponsor to take into account the potential for usage in adjuvant hormonal treatment of early breast cancer extending beyond 3 years for exemestane (or 5 years in total), for which there is no evidence. The PBAC also advised the PBPA that the aromatase inhibitors should remain listed on a cost-minimisation basis overall.

Recommendation

Add to the existing listing:

Restriction: Restricted benefit

Treatment of hormone-dependent early breast cancer in post-menopausal women following a minimum of 2 years treatment with tamoxifen citrate.

NOTE:

This drug is not PBS-subsidised for adjuvant hormonal treatment of early breast cancer extended beyond 5 years, i.e. a patient who has received 2 years of tamoxifen therapy may only receive 3 years of PBS subsidised treatment with exemestane.

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 entered into a risk sharing arrangement with the Commonwealth.