PUBLIC SUMMARY DOCUMENT
Product: Everolimus, tablet, 5 mg and 10 mg, Afinitor®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested an Authority required listing for treatment, in combination with an aromatase inhibitor, of post-menopausal women with hormone-receptor positive, HER2 negative advanced breast cancer after failure of treatment with letrozole or anastrozole.

2. Background

The PBAC had not previously considered everolimus for this indication.

3. Registration Status

The submission was received under the TGA/PBAC Parallel Process provisions. At the time of PBAC consideration, the Clinical Evaluation Report, TGA Delegate's Overview and ACPM outcome were available.

Everolimus was registered by the TGA on 25 Feb 2013 as follows:

- For the treatment of postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

Everolimus is also registered by the TGA for the following indications.

- For the treatment of patients with advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.
- For the treatment of patients with progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETS) of pancreatic origin.
- For the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS), who require therapeutic intervention but are not candidates for curative surgical resection.

4. Listing Requested and PBAC's View

Authority required (Section 85)

Treatment, in combination with an aromatase inhibitor, of post-menopausal women with hormone-receptor positive, HER2 negative advanced breast cancer after failure of treatment with letrozole or anastrozole.

Note: Everolimus is to be discontinued following progression of disease.

The PBAC noted that the regulatory application for everolimus for the extension of indications to include treatment of HER2 negative advanced breast cancer was considered by the Advisory Committee on Prescription Medicines (ACPM) at its February 2013 meeting. The ACPM considered everolimus to have a positive risk-benefit profile for the above mentioned indication.

The PBAC considered that any PBS listing for everolimus should have restriction wording consistent with the TGA-approved indication.

5. Clinical Place for the Proposed Therapy

The presence of the oestrogen receptor (ER) and/or progesterone receptor (PgR) is an important predictive and prognostic marker and approximately 70% of all invasive breast cancers are ER and/ or PgR positive at the time of diagnosis. Currently, a sequential endocrine therapy approach is accepted in Australia for the majority of patients with hormone receptor positive advanced breast cancer. In those patients previously treated with a non-steroidal aromatase inhibitor (NSAI), the submission proposed that everolimus is added to the current aromatase inhibitor (AI) to overcome AI resistance. The proposed clinical algorithm assumed all AI's equal in endocrine therapy cascade. This was not considered appropriate by the PBAC.

For PBAC's view, see Recommendation & Reasons.

6. Comparator

The submission nominated 'any AI' (letrozole, anastrozole or exemestane) as the main comparator.

The PBAC noted the different mechanisms of action of steroidal and non-steroidal AIs. The PBAC considered that it was not possible to extrapolate the effectiveness of everolimus in combination with exemestane (a steroidal AI) to inform an assessment of the effectiveness of everolimus in combination with letrozole or anastrazole (non-steroidal AIs).

For PBAC's view, see Recommendation & Reasons.

7. Clinical Trials

The submission presented one randomised trial (BOLERO-2) comparing everolimus + exemestane with placebo + exemestane in 724 post-menopausal patients with ER positive and HER2 negative advanced breast cancer.

Publication details of BOLERO-2 are presented in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
BOLERO-2	Novartis drug Afinitor helps women with advanced breast cancer live significantly longer without their disease progressing.	Onkol 2011; 5 (5): 311.
	Everolimus for postmenopausal women with advanced breast cancer: Updated results of the BOLERO-2 Phase III Trial	Clin Adv Hematol Oncol 2012; 10 (2): 4-6
	Abstract Book EBCC8 - European Breast Cancer Conference.	Eur J Cancer 2012; 48
Baselga J, et al.	Everolimus in combination with exemestane for postmenopausal women with advanced breast cancer who are refractory to letrozole or anastrozole: Results of the BOLERO-2 phase III trial.	J Clin Oncol 2011b; 29 (15)
Baselga J, et al.	Everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor-positive metastatic	J Clin Oncol 2011b; 29 (15)

Trial ID/ First author	Protocol title/ Publication title	Publication citation
	breast cancer who are refractory to letrozole or anastrozole: Preliminary results of the BOLERO-2 trial	
Baselga J, et al.	Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.	New Engl J Med 2012: 366 (6): 520-9
Brunk D.	BOLERO-2: Everolimus plus exemestane doubles PFS	Oncol Rep 2012; 7
Campone M, et al.	Bolero-2: Everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor-positive advanced breast cancer refractory to letrozole or anastrozole.	Breast 2011; 20 S30
Gnant M, et al.	Everolimus added to exemestane reduced bone markers in postmenopausal women with advanced breast cancer (ABC): The bolero-2 trial.	Eur J Cancer 2012a; 48 S43
Gnant M, et al.	Everolimus added to exemestane reduced bone markers and disease progression in bone in postmenopausal women with advanced breast cancer: Updated results from the bolero-2 trial.	Eur J Cancer 2012b; 48 S2
Kasprowicz N, et al.	Evaluation of RAD001 (everolimus) in the setting of resistance to letrozole or anastrozole in postmenopausal ER-positive breast cancer patients: BOLERO-2 trial.	Arch Gynecol Obstet 2010; 282 S126
Rugo H, et al.	Everolimus (EVE) for postmenopausal women with advanced breast cancer (ABC) refractory to letrozole or anastrozole: Long-term efficacy and safety results of the bolero-2 trial.	Eur J Cancer 2012; 48 S116

The PBAC expressed concern that whilst the trial provided evidence for the effectiveness of everolimus in combination with exemestane, the requested restriction was for use with any AI. The PBAC considered use with a different AI may result in different effectiveness and toxicities. However, the PBAC noted that the ACPM had supported registration of everolimus only in combination with exemestane.

8. Results of Trials

The results for progression free survival (PFS) and overall survival (OS) from BOLERO-2 are presented in the following tables.

Results of PFS in BOLERO-2

	Everolimus +Exemestane N=485	Exemestane + Placebo N=239
PFS assessment as per investigator		
No. of PFS events, n (%)	310 (63.9)	200 (83.7)
Progression	294 (60.6)	198 (82.8)
Death before progression	16 (3.3)	2 (0.8)
Censored (including ongoing	175 (36.1)	39 (16.3)

	Everolimus +Exemestane N=485	Exemestane + Placebo N=239
participants), n (%)		
PFS (months), median (95% CI)	7.82 (6.93, 8.48)	3.19 (2.76, 4.14)
Improvement in median PFS	4.63	
Hazard ratio (95% CI)	0.45 (0.38, 0.54)	
p value[a]	p<0.0001	
Risk difference[b] (95% CI)	-0.20(-0.26, -0.13)	

Abbreviations: CI, confidence interval; PFS, progression-free survival.
Note: [a] No formal significance testing was conducted as the primary endpoint was met at the first interim analysis but p-values are included here to demonstrate the strength of evidence in favor of treatment with everolimus plus exemestane.
[b] Calculated during the evaluation

Results of OS in BOLERO-2

	Everolimus +Exemestane N=485	Exemestane + Placebo N=239
No. of deaths, n (%)	112 (23)	70 (29)
No. censored, n (%)	373 (77)	169 (71)
Median OS in months (95% CI)	NR (20.7, NR)	NR (NR, NR)
Hazard ratio[a] (95% CI)	0.77 (0.57, 1.04)	
One-sided p value[b]	P=0.046	
Risk difference[c] (95% CI	-0.06(-0.13, 0.01)	

Abbreviations: CI, confidence interval; FAS, full set analysis; OS, overall survival; NR, not reached
Notes: [a] Hazard ratio is obtained from stratified Cox model.
[b] P value is obtained from the stratified one-sided log-rank test. Calculated during the evaluation

The PBAC noted that final PFS analysis was conducted in December 2011 and considered that more recent estimates of the gain in PFS would be useful when making subsidy decisions. This was also true for estimates of the gain in OS. The PBAC noted that the size of the treatment effect was currently extremely uncertain due to the immature data on overall survival.

The submission, in its pre-subcommittee response (PSCR), acknowledged that no statistically significant treatment related difference had thus far been demonstrated, but stated that a difference in the percentage of OS events (favouring the everolimus combination arm) was demonstrated at each data cut-off date. The PSCR stated that the magnitude of this difference has increased over time, suggesting a treatment effect on OS.

The PBAC noted that both progression free survival (PFS) and overall survival (OS) outcome data were used in the economic evaluation. The PBAC considered the lack of mature data for OS was a major limitation estimating the survival benefit and any modelled survival benefit was extremely uncertain.

The submission provided a summary of results of safety outcomes from BOLERO-2. The everolimus + exemestane arm had significantly more adverse events than the placebo +exemestane arm for all outcomes reported, except for deaths and on-treatment deaths. The most commonly reported grade 3 or 4 adverse events experienced by patients in the everolimus plus exemestane arm were stomatitis, dyspnoea, anaemia and hyperglycaemia.

For PBAC's view, see Recommendation & Reasons.

9. Clinical Claim

The submission described everolimus in combination with an AI (exemestane) as superior in terms of comparative effectiveness with a 'higher but manageable toxicity profile', when compared to an AI (exemestane). The PBAC considered that this claim was not adequately supported.

For PBAC's view, see Recommendation & Reasons.

10. Economic Analysis

The submission presented a modelled economic evaluation (cost-utility analysis) based on the claim of superior efficacy using trial based PFS and OS, extrapolated to 7 years. The evaluation was structured as a three state Markov-like model with two alternative treatment pathways (Everolimus + AI) and AI only. The three health states were stable disease, progressive disease and dead.

The base case ICER was revised in the submission's PSCR to be between $45,000 - $75,000/QALY, corrected for the omission of adverse events of pneumonitis and fatigue from the economic model. The revised ICER also took into account an adjustment in the dose duration used. The PBAC considered the ICER to be unacceptably high and uncertain.

Key drivers of the model were:

- Modelled OS forecasts/projections and associated transition probabilities.
- Time horizon: It is assumed that the treatment effect continues beyond the trial period of 96 weeks to 7 years duration.
- The cost of everolimus.

Key sensitivity analyses indicated that the ICER could be substantially higher.

The PBAC noted that the submission relied on an interim analysis of the BOLERO-2 trial, at which point OS data were not mature. The PBAC considered therefore that the extrapolation of PFS into OS in the model was of concern and could not be relied upon. The PBAC noted that final PFS analysis was conducted in December 2011 and considered that a more recent estimate of the gain in PFS and in OS may be informative in providing a more robust basis for estimating the benefits of treatment. Alternatively, although noting that a 7 year time horizon would ordinarily be appropriate for an intervention of this type, the model may be rerun with a time horizon of 3 years to eliminate the uncertainty in the overall survival benefits of everolimus for this indication.

The PBAC noted also the sensitivity of the model to the cost of everolimus and considered that the price was not adequately supported by the data presented.

The PBAC noted that the economic model assigned a utility of 0.874 to patients with stable disease beginning treatment and 0.435 to patients with progressive disease on chemotherapy, based on a recent meta-regression of breast cancer health state utilities by Peasgood et al (2010). The PBAC noted that Lloyd et al (2006) estimates a utility of 0.715 for stable disease. The PBAC noted also that the baseline characteristics reported by the submission were incomplete and suggested that the BOLERO-2 trial patients may be healthier than the intended PBS population.

The PBAC noted that although the model included costs for adverse events, no utility decrements were included. In particular, the PBAC noted that the model did not capture specific adverse events relevant to everolimus, such as fatigue. The PBAC noted estimates in Lloyd et al (2006) for decrements due to adverse events ranging between 0.103 and 0.150.

The PBAC considered that in light of the available data and the high rates of adverse events reported for everolimus in the BOLERO-2 trial, omission of utility decrements inappropriately favours everolimus.

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost to the PBS to be $30 - $60 million over the first 5 years.

12. Recommendation and Reasons

The PBAC rejected the submission on the basis of uncertain clinical benefit, in terms of overall survival, and high and uncertain cost effectiveness. The PBAC considered that the critical issue with the submission was that the overall survival data from the trial were too immature to inform a decision. In the absence of more mature data, the PBAC considered the modelled survival benefits were probably overestimated as was the utility gain.

The PBAC considered that the submission's proposed clinical algorithm was not appropriate as it:

i. Did not consider cross-class resistance between steroidal and non-steroidal AIs;
ii. Considered all AIs are equivalent when used in sequence with everolimus;
iii. Did not consider that exemestane is currently listed for second line therapy (after use with tamoxifen).

The PBAC considered that exemestane may be an appropriate comparator in view of the clinical evidence presented in the submission, but that this was not consistent with the proposed PBS restriction which would allow the use of everolimus in combination with any AI.

The PBAC considered the clinical claim was not adequately supported. The PBAC considered it was uncertain as to whether superiority in progression free survival (PFS) would translate into an overall survival (OS) advantage. The PBAC considered the OS data was too immature to provide a reliable estimate of survival. The PBAC considered the claim of a 'higher but manageable toxicity profile' was reasonable.

The PBAC noted that the trial data supported the claim of comparative effectiveness of everolimus in combination with exemestane only. The PBAC considered that it was not possible to extrapolate this to comparative effectiveness of everolimus in combination with any AI.

The PBAC further considered that the final analysis of OS from BOLERO-2 would be informative should be included in any future re-submission.

The PBAC noted that the submission is eligible for an Independent Review.

The PBAC noted the consumer comments received in relation to the submission.

Recommendation:
Rejected

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.