Public Summary Document

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

1. Purpose of Application

The resubmission sought an Authority required listing for treatment, with everolimus in combination with exemestane, of post-menopausal women with hormone-receptor positive, HER2 negative advanced breast cancer after failure of letrozole or anastrozole.

2. Background

This was the second submission requesting listing of everolimus for the above indication.

At its March 2013 meeting, the PBAC rejected a submission seeking 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.

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 issues with the submission were the request for use of everolimus in combination with any aromatase inhibitor rather than only with exemestane and 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.

For further details, refer to the March 2013 PBAC Public Summary Document available at http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-03/everolimus.

3. Registration Status

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 of pancreatic origin.
- For the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis, who require therapeutic intervention but are not candidates for curative surgical resection.

4. Listing Requested and PBAC's View

The following amendments to the requested restriction presented in the March 2013 PBAC submission were proposed:
(Changes appear in italics and strikethrough)

Authority required
~~Treatment, in combination with an aromatase inhibitor,~~ *For the treatment* of post-menopausal women with hormone-receptor positive, HER2 negative advanced breast cancer *in combination with exemestane* after failure of treatment with letrozole or anastrozole.
~~Note: Everolimus is to be discontinued following progression of disease.~~

The PBAC considered that the restriction should retain a requirement that everolimus be discontinued upon disease progression.

Consistent with the final TGA-approved indication 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, the PBAC considered that the restriction should allow only combination with exemestane, and not permit use with *any* aromatase inhibitor.

The PBAC considered that the evidence did not support the use of everolimus in patients with oestrogen receptor positive breast cancer who were naïve to aromatase inhibitors or had primary (*de novo)* endocrine resistance disease. A combination of everolimus and exemestane would only be clinically appropriate where the patient had acquired endocrine resistance following a demonstrated response to an aromatase inhibitor (letrozole or anastrozole).

5. Clinical Place for the Proposed Therapy

The resubmission proposed everolimus "…*for the treatment of post-menopausal women with hormone-receptor positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole".*

The resubmission amended the place in therapy from the March 2013 submission, in that it proposed everolimus specifically in combination with exemestane. The March 2013 submission had proposed the use of everolimus with any aromatase inhibitor.

The PBAC considered that everolimus would be used in combination with exemestane.

6. Comparator

The March 2013 submission had proposed any aromatase inhibitor (letrozole, anastrozole or exemestane) as the main comparator.

The minor resubmission did not explicitly change the comparator, although the proposed restriction had been amended to explicitly include only exemestane.

The PBAC had previously considered that exemestane was the appropriate comparator.

7. Clinical Trials

No new clinical data were included in the submission.
Please refer to the March 2013 Public Summary Document for details of trials presented in the previous submission.

8. Results of Trials

No new data relating to comparative effectiveness or comparative harms were included in the submission.

The PBAC recalled from March 2013 that it requested the sponsor provide updated overall survival data from the BOLERO-2 trial.

9. Clinical Claim

The clinical claim was unchanged from the March 2013 submission.

10. Economic Analysis

The resubmission presented a revised economic analysis based on a reduced price of everolimus and a shorter 3-year horizon model.

The resubmission offered a price reduction (for both tablet strengths).

The resubmission presented a revised ICER in the range $45,000 - $75,000, based on a reduced price and a shorter 3-year time horizon model. The revised ICER was within the same range but higher than the ICER presented in the March 2013 PBAC submission with a 7-year time horizon model.

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost to the PBS to be $10 million - $30 million in Year 5.

The PBAC considered that as the data supporting the use of everolimus for breast cancer were not currently mature, utilisation would be driven by future emerging evidence and would therefore be unpredictable. The PBAC therefore considered that a cap would be required to contain the financial risk to the Commonwealth.

The resubmission requested a Special Pricing Arrangement.

12. Recommendation and Reasons

The PBAC deferred the submission to allow the Department to negotiate with the sponsor a price in line with an ICER that would recognise the value of everolimus for this indication while at the same time acknowledging the lack of overall survival data. The PBAC acknowledged the price reduction offered by the sponsor, however considered that a further reduction to achieve an ICER below $60,000/QALY would be required.

The PBAC agreed that the restriction should specifically refer to combination with exemestane. In addition, the PBAC considered that the restriction should preclude use of everolimus beyond disease progression, and that everolimus should not be used for aromatase

inhibitor naïve, oestrogen receptor positive breast cancer. The role of everolimus was to restore the sensitivity of estrogen receptor positive cancers to endocrine therapy. For this reason, a combination of everolimus and exemestane would only be clinically appropriate where the patient has previously demonstrated a response to a non-steroidal aromatase inhibitor (such as letrozole or anastrozole).

The PBAC noted that the restriction for exemestane currently includes *"Treatment of hormone-dependent advanced breast cancer in post-menopausal women with disease progression following treatment with tamoxifen citrate"* and *"Treatment of hormone-dependent early breast cancer in post-menopausal women following a minimum of 2 years treatment with tamoxifen citrate"*. The PBAC noted that the restriction for exemestane would require review should everolimus be PBS listed for this indication.

The PBAC considered that should everolimus be PBS listed, a written Authority would be appropriate.

The PBAC requested that the sponsor provide overall survival data from the BOLERO-2 trial when it is available.

The PBAC advised that, under Section 101(3BA) of the *National Health Act 1953*, there are no therapies which are considered interchangeable with everolimus on an individual patient basis.

The PBAC considered that, should everolimus be PBS listed, it would not be appropriate for nurse practitioner prescribing.

Following advice of the PBAC's deferral, the sponsor offered an additional price reduction off the original dispensed price for the maximum quantity, bringing the ICER lower within the $45,000 - $75,000/QALY range. The PBAC considered this acceptable and recommended out of session approval of everolimus for breast cancer, in combination with exemestane.

Outcome:
Recommended

Recommended listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
EVEROLIMUS			
Tablet 5mg	30	5	Afinitor NV
Tablet 10mg	30	5	Afinitor NV

Condition/Indication:	Advanced breast cancer
Restriction:	Authority required TO BE FINALISED

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 welcomes the positive recommendation by the PBAC and looks forward to finalising the details for the PBS listing of everolimus in advanced breast cancer.