**PUBLIC SUMMARY DOCUMENT**
**Product:** Everolimus, tablets, 5 mg and 10 mg, Afinitor®
**Sponsor:** Novartis Pharmaceuticals Australia Pty Ltd
**Date of PBAC Consideration:** November 2011

## 1. Purpose of Application

To seek an Authority Required listing for initial and continuing treatment of Stage IV clear cell variant renal cell carcinoma in a patient with a WHO status of 2 or less, who has failed treatment with sunitinib.

## 2. Background

This was the fourth submission for everolimus requesting listing for clear cell renal carcinoma.

At the November 2009 meeting, the PBAC rejected a submission for everolimus for treatment, as the sole PBS-subsidised therapy, of a patient with Stage IV clear cell variant renal cell carcinoma after failure of treatment with sorafenib or sunitinib on the basis of uncertain clinical benefit and a high and uncertain cost-effectiveness ratio.

*For full details, see November 2009 Public Summary Document.*

At its July 2010 meeting, the PBAC rejected a re-submission on the basis of uncertain clinical benefit and a high and uncertain cost-effectiveness ratio.

*For full details, see July 2010 Public Summary Document.*

At the November 2010 meeting, the PBAC rejected a minor re-submission on the basis of a high and uncertain cost-effectiveness ratio. The PBAC considered that despite the clinical need and trial-based evidence of improved PFS, the magnitude of the clinical benefit in relation to survival was uncertain and that with plausible survival modelling, the ICER remained unacceptably high.

## 3. Registration Status

Everolimus tablets 5 mg and 10 mg were registered by the TGA on 29 July 2009 for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.

## 4. Listing Requested and PBAC's View

Authority Required

Initial treatment, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who has failed treatment with sunitinib and has a WHO status of 2 or less.

Failure of treatment with sunitinib is defined as:
*(i)* Progressive disease as defined by the RECIST criteria; or
*(ii)* Toxicity that is sunitinib related and necessitates permanent cessation of sunitinib.

NOTES:
Everolimus should not be used after disease progression on temsirolimus.
RECIST criteria are defined as follows:
Complete response (CR) is disappearance of all target lesions.
Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.
Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.

Stable disease (SD) is small changes that do not meet above criteria.

No applications for increased maximum quantities and/or repeats will be authorised.

Authority Required
Continuing treatment beyond 3 months, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who has previously been issued with an authority prescription for everolimus and who has stable or responding disease according to the RECIST criteria.

NOTES:
Everolimus should not be used after disease progression on temsirolimus.

RECIST criteria are defined as follows:
Complete response (CR) is disappearance of all target lesions.
Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.
Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.
Stable disease (SD) is small changes that do not meet above criteria.

No applications for increased maximum quantities and/or repeats will be authorised.

Authority Required (grandfather)
Initial treatment, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) after failure of treatment with sunitinib in a patient who was receiving treatment with everolimus prior to (insert LISTING DATE).

Failure of treatment with sunitinib is defined as:
*(i)* Progressive disease as defined by the RECIST criteria; or
*(ii)* Toxicity that is sunitinib related and necessitates permanent cessation of sunitinib.

NOTES:
Everolimus should not be used after disease progression on temsirolimus.

RECIST criteria are defined as follows:
Complete response (CR) is disappearance of all target lesions.
Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.
Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.
Stable disease (SD) is small changes that do not meet above criteria.

No applications for increased maximum quantities and/or repeats will be authorised.

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy

Renal cell carcinoma (RCC) is a form of kidney cancer that arises from the cells of the renal tubule. The management and prognosis of a patient with RCC is determined by the stage of the disease. Surgery is the only curative treatment option for localised RCC – radical nephrectomy is considered the gold-standard treatment for all patients with localised tumours. In patients with locally advanced or metastatic disease, nephrectomy may also be considered. As RCC progresses, the tumour grows and enlarges, and often spreads to adjacent organs. However, most patients are diagnosed with advanced RCC which is often refractory to treatment and associated with a poor prognosis.

Currently, only sunitinib is PBS listed for this indication. The submission proposed that everolimus would be a new treatment option for patients with advanced RCC who have failed sunitinib.

## 6. Comparator

Best supportive care (BSC) was nominated as the comparator. This was previously considered appropriate by the PBAC.

## 7. Clinical Trials

No changes had been made to the trial data previously presented from the RECORD-1 trial, a randomised trial comparing everolimus, 10 mg per day orally, with placebo in patients with metastatic clear cell carcinoma (mRCC) with Karnofsky performance score of at least 70 and previous progression on, or within six months of treatment with, sunitinib and/or sorafenib. The primary clinical outcome was progression-free survival (PFS), and patients in the placebo arm could cross-over to everolimus after progression.

One additional publication (Motzer et al 2010) arising from the RECORD-1 trial was identified in an updated literature search, see below:

| Trial ID/ First author | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Direct randomised trial(s)** | | |
| RECORD-1 | | |
| Motzer R et al. | Phase 3 trial of everolimus for metastatic renal cell carcinoma. Final results and analysis of prognostic factors. | Cancer 2010; 116 (18):4256-4265. |

## 8. Results of Trials

The PBAC recalled that everolimus demonstrated a statistically significant improvement in progression-free survival (PFS) (HR: 0.33, 95% CI: 0.25, 0.43) compared with placebo but the extent of the benefit, three months, was small. The overall survival (OS) data for the intention-to-treat population demonstrated no statistically significant difference for everolimus compared with placebo, with a hazard ratio 0.87 (95% CI: 0.65-1.17). As previously noted, this result was biased towards no treatment effect because the RCT was designed to allow for switching to everolimus on progression. That is, the result for OS is confounded by the extensive (77%) cross-over of placebo patients to everolimus at progression.

The PBAC also noted that the RECORD-1 trial did not demonstrate a statistically significant benefit for everolimus compared with placebo in terms of other secondary outcomes, including quality of life. However, these results are also confounded by the extensive (77%) cross-over of placebo patients to everolimus at progression.

No new toxicity data were presented in the re-submission and the safety assessment of the RECORD-1 trial had not been updated.

## 9. Clinical Claim

The re-submission claimed everolimus has superior efficacy and inferior safety in mRCC compared with placebo.

The PBAC considered that the main uncertainty was whether there is a survival gain associated with treatment with everolimus and if so, the magnitude of the gain. The PBAC

noted that the clinical importance of the PFS gain had not been demonstrated in terms of improvements in the symptoms of RCC.

The PBAC had previously considered that the re-submission's claim of inferior safety of everolimus compared with placebo was reasonable.

**10. Economic Analysis**

An updated modelled economic evaluation was presented.

The submission presented additional UK historical control survival data and a revised extrapolation method to derive overall survival curves for the placebo arm to be used in the modelled economic evaluation.

The base case ICER (time horizon 5 years) using the Rank Preserving Structural Failure Time method (RPSFT) was calculated to be between $45,000 - $75,000 per QALY.

*For PBAC's view, see Recommendation and Reasons.*

**11. Estimated PBS Usage and Financial Implications**

The likely number of patients treated was estimated by the submission to be less than 10,000 over the first 5 years. The estimation was considered uncertain due to uncertainty in the projected sunitinib patient numbers and uncertainty in the proportion of sunitinib patients eligible for everolimus.

The net financial cost to the PBS was estimated by the submission to be less than $10 million in Year 5. The estimation was considered uncertain.

**12. Recommendation and Reasons**

The PBAC noted it had previously accepted that BSC was the appropriate comparator. The PBAC recalled that in July 2010 there was uncertainty about a conclusion of superior efficacy in mRCC with everolimus compared with placebo based on the benefit in terms of PFS, when no benefit in terms of OS or quality of life was observed in RECORD-1. Based on the supporting data the claim for inferior safety was considered reasonable.

The PBAC noted there were no new trial data provided in the re-submission. However, the submission presented additional UK historical control survival data and a revised extrapolation method to derive overall survival curves for the placebo arm to be used in the modelled economic evaluation. The results of this survival analysis were compared with community-based survival data sourced from Medicare on sunitinib patients, to further validate the UK data's applicability to the Australian population. There was also an update (in the manuscript form) of the systemic review by Delea et al to estimate the ratio of incremental OS benefit to incremental PFS.

The PBAC noted that the sunitinib data show survival appears worse in the community than in the trial (Motzer et al 2010), highlighting that trial results may overestimate the benefit of therapy. The PBAC considered that these additional data had increased rather than decreased the uncertainty regarding survival by indicating that the time horizon of 5 years may be too optimistic.

The PBAC also noted that the study population for everolimus is a combination of failed TKIs (sunitinib) and patients who have never been exposed to an effective TKI (sorafenib). The PBAC has previously noted that sorafenib has failed to show any benefit as a first line agent in RCC, and hence this may have influenced the benefit observed for everolimus.

The base case ICER (time horizon 5 years) using the RPSFT was calculated to be between $45,000 - $75,000 per QALY in the current re-submission.

The PBAC noted the results of the sensitivity analyses indicate that the model is most sensitive to the model duration due to the relatively large proportion of the QALY gain extrapolated to occur beyond the duration of the trial. The PBAC noted that in calculating the ICERs there is an assumption that treatment would be ceased on progression, which may not happen in clinical practice as everolimus is administered orally. Also, clinicians may not routinely monitor patients with scans to detect progression at this stage of the disease. Therefore, the PBAC considered that the ICERs could potentially be higher.

The PBAC accepted that there is a high clinical need for alternative therapies for renal cancer. However, the main uncertainty for the PBAC is whether there is a survival gain associated with this drug and if so, the magnitude of the gain. The PBAC noted that the clinical importance of the PFS gain has not been demonstrated in terms of improvements in the symptoms of RCC.

Therefore, the PBAC rejected the submission on the basis of a high and uncertain cost-effectiveness ratio.

The PBAC acknowledged and noted the consumer comments on this item.

***Recommendation***:
**Reject**

## 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.