PUBLIC SUMMARY DOCUMENT
Product: EVEROLIMUS, tablets, 5 mg and 10 mg, Afinitor®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought an Authority Required listing for the 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 progressive disease on sunitinib or progressive disease following cessation of treatment with sunitinib due to toxicity and meets certain criteria.

2. Background

At the November 2009 meeting, the PBAC rejected the 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.

Full details in the November 2009 Public Summary Document.

3. Registration Status `

Everolimus was designated an orphan drug by the TGA on 17 July 2008.

Everolimus tablets 5 mg and 10 mg were TGA registered 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 with a WHO status of 2 or less who has:
(i) Progressive disease (as defined by the RECIST criteria) on sunitinib treatment; or
(ii) Progressive disease (as defined by RECIST criteria) following permanent cessation of sunitinib treatment due to toxicity that was sunitinib related.

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:
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) in a patient who was receiving treatment with everolimus prior to (insert LISTING DATE) and who had:

(i) Progressive disease (as defined by the RECIST criteria) on sunitinib treatment; or
(ii) Progressive disease (as defined by RECIST criteria) following permanent cessation of sunitinib treatment due to toxicity that was sunitinib related.

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.

The PBAC did not comment on the requested restriction.

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. Everolimus would be a new treatment option for patients with advanced RCC who have failed sunitinib.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

As previously, the re-submission appropriately nominated placebo for best supportive care as the comparator.

7. Clinical Trials

The submission presented key clinical evidence from the RECORD-1 trial, a randomised trial comparing everolimus, 10mg 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. The PBAC noted that the resubmission provided updated overall survival evidence for RECORD-1.

Details of the published reports included in the submission are in the table below:

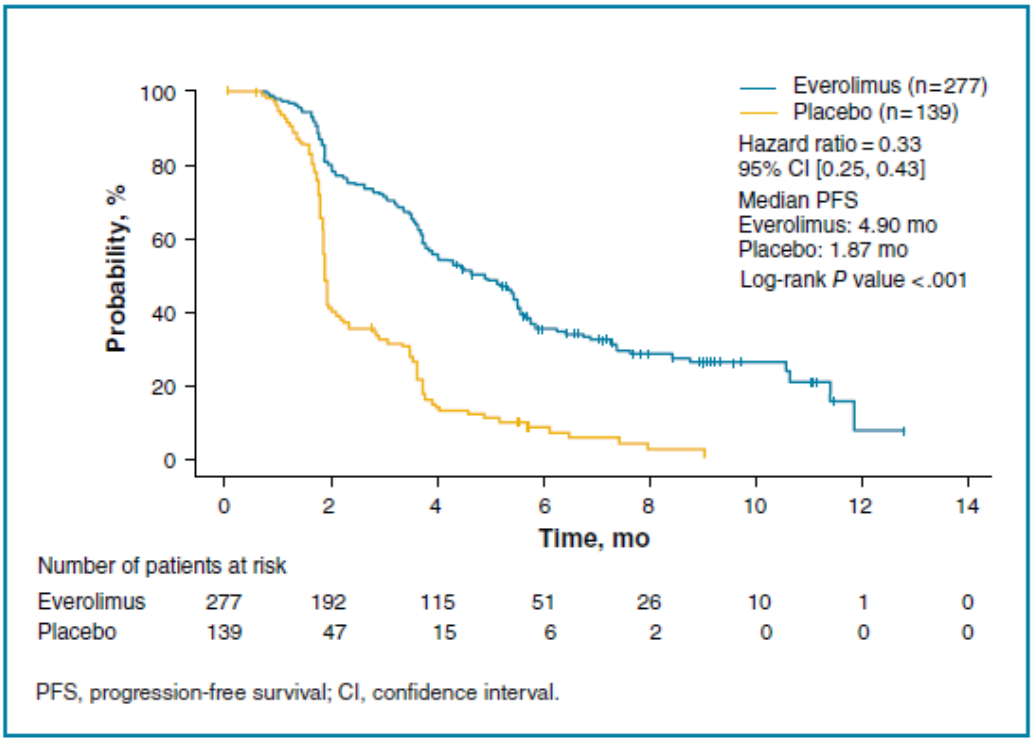
Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Motzer R et al. 2008	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial	Lancet 2008; 372(9637):449-56
Korhonen P et al. 2009	Overall survival among metastatic renal cell carcinoma patients corrected for cross-over using a Rank Preserving Structural Failure Time (RPSFT) Model: analyses from the RECORD-1 Phase 3 trial.	Presented at the Joint 15th Congress of the European Society for Medical Oncology (ESMO), 20-24 September 2009, Berlin, Germany

8. Results of Trials

The primary outcome for the study was progression free survival (PFS).

Everolimus showed a statistically significant improvement in progression free survival (PFS) (HR: 0.33, 95% CI: 0.25, 0.43) but the extent of the benefit, three months, was small.

The Kaplan Meier probability of progression free survival curve is shown below:

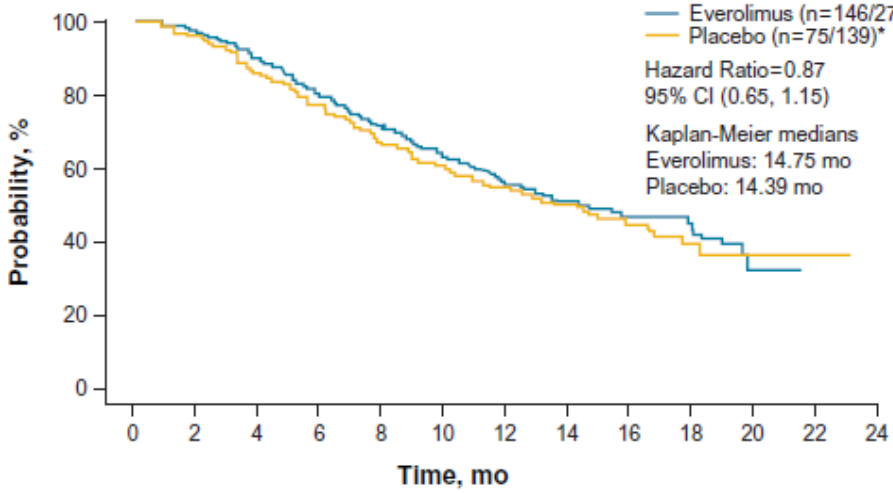


The updated overall survival (OS) data to November 2008 for the intention-to-treat population showed no statistically significant difference for everolimus, with a hazard ratio 0.87 (95% CI: 0.65-1.15).

Overall survival (OS) data to October 2007 presented in the previous submission also showed no statistically significant difference between everolimus and placebo (HR 0.83, 95% CI: 0.50, 1.37).

The PBAC noted that the results indicate that over time the HR is getting closer to the null (1.0).

The updated Kaplan Meier curve is shown below:



Number of patients at risk

Everolimus	277	267	243	213	190	166	147	121	77	41	8	0	0
Placebo	139	131	118	103	89	79	68	57	33	17	4	1	0

CI, confidence interval.
*112/139 patients randomized to placebo were treated with everolimus; 106 crossed over before the end of the double blind phase and additional 6 patients after the study unblinding.

For PBAC's view, see Recommendation and Reasons.

An exploratory post-hoc analysis of censored data, which excluded the patients who crossed over to active treatment, was provided in the CHMP D120 report as an appendix to the re-submission. The resultant HR for overall survival was insignificant at 0.67 (95% CI 0.39-1.14, p=0.069). This analysis would strongly favour everolimus, since patients with progressed disease in the placebo arm who do not cross-over may have more advanced disease and require palliative care rather than further active treatment. A similar analysis with the sunitinib data showed strongly significant benefits of treatment, with a doubling in median overall survival for sunitinib compared with interferon treated patients (28 months v 14 months, respectively, HR 0.65 95% CI 0.48-0.87, p=0.03) (Motzer et al., 2009).

The safety assessment of the RECORD-1 trial was not updated in this re-submission.

During the evaluation relative risks and risk differences were calculated for Grade 3/4 adverse events occurring in ≥2% of either treatment group.

Everolimus patients were significantly more likely to experience hyperglycaemia, stomatitis, anaemia, dyspnoea, vomiting, hypercholesterolemia, pneumonitis and lymphopenia, as measured by the risk difference. In addition, discontinuation from treatment, primarily due to adverse effects, was more common in everolimus patients (13.1%) than placebo patients (1.5%).

9. Clinical Claim

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

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

An updated cost-utility analysis was presented.

The model took the form of a Markov process with three health states-stable disease, progressive disease and death and had an 8-year horizon.

The costs were updated to include the costs of palliative care in progressed disease.

The previous submission reported an incremental cost-effectiveness ratio of between $45,000 and $75,000 for everolimus, calculated using the inverse censoring probability weighted (IPCW) method. This was compared with a lower ICER within the same range in the current re-submission. The main reasons for the improved cost-effectiveness of everolimus when modelled with the current model include:

- modelling of overall survival used lower mortality risks beyond trial duration for both everolimus and placebo (5.4% and 10.7%, per monthly cycle, respectively), compared with the previous model (44% and 81%, per 2 month cycle, respectively); and
- the increased time horizon (increased from three years to eight years), which captures the higher overall survival, without appropriately modelling the associated increased costs from extended time in progressed disease

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated by the re-submission to be less than 10,000 in Year 5, which was less than the previous submission's estimate, but within the same range.

The financial cost per year to the PBS was estimated by the re-submission to be less than $10 million in Year 5, compared with the previous submission's estimate of between $10 million and $30 million by Year 5.

12. Recommendation and Reasons

The PBAC acknowledged that there is a high clinical need for treatment of patients who have progressed on sunitinib or those who are ineligible or intolerant to sunitinib.

As previously, the PBAC agreed that the comparator of placebo for best supportive care is appropriate.

The submission presents key clinical evidence from the RECORD-1 trial, a randomised trial comparing everolimus, 10mg 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. The PBAC noted that the resubmission provided updated overall survival evidence for RECORD-1.

The PBAC considered that RECORD-1 was a well conducted trial and noted that everolimus showed a statistically significant improvement in PFS (HR: 0.33, 95% CI: 0.25, 0.43) but also that the extent of the benefit, three months, was small. The PBAC considered that in the absence of direct trial-based evidence for either prolonged survival or improved quality of life, the clinical importance of a PFS benefit of 3 months was highly uncertain. The PBAC noted that the advice from the oncologists included in the Pre-Sub-Committee Response referred to other cancers where PFS has been proven as a surrogate for overall survival, but that this relationship has not been established for mRCC. In addition there was no evidence provided that the radiological measure used to determine progression was of direct patient relevance or could be extrapolated into survival in this setting.

The updated overall survival (OS) data to November 2008 for the intention-to-treat population showed no statistically significant difference for everolimus, with a hazard ratio 0.87 (95% CI: 0.65-1.17). The PBAC considered that because of the high rate of cross-over of patients to everolimus (77%) the trial provided no information for life expectancy of patients treated with best supportive care (BSC) only. The updated information also did not demonstrate a statistically significant benefit of everolimus in terms of other secondary outcomes, including quality of life. However, these results are also confounded by the cross-over of placebo patients to everolimus at radiological progression.

The PBAC considered that 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 agreed with the sponsor's Pre-Sub-Committee Response that it was appropriate to use data from the entire trial rather than just the sunitinib-treated subgroup because there was a constant hazard ratio across the patient populations and there was a statistically significant advantage shown in each subgroup which was maintained.

The PBAC noted that the monthly mortality risk (5.4%) for patients in the everolimus group was calculated from the overall survival in the RECORD-1 trial. This is considerably lower than the risk modelled in the previous submission, which implied a 44.4% risk for each two month cycle in the extrapolated period of the model. As a result, patients are estimated to live longer in the updated model. One percent of the everolimus-treated population is still alive at the beginning of cycle 83 (6.9 years) and 0.38% at the beginning of cycle 101 (8.3 years). The PBAC noted that this approach resulted in some patients remaining alive after 8 years which seemed improbable.

The PBAC considered that the modelled claim of a 4-7 month overall survival advantage for everolimus was improbable, given that (i) the extent of gain in overall survival beyond the effect on PFS (3 months in ITT and 2.1 months in sunitinib pretreated population) is unlikely, (ii) the weighting given to the early (2 month) cross over data, and (iii) the toxicity of everolimus. The modelled estimates using IPCW and RPSFT models are also inherently confounded by the design limitations of RECORD-1 which permitted an early and extensive crossover of patients between the trial arms

The PBAC noted that the model was very sensitive to changes in the assumed overall survival benefit of everolimus and the estimated ICERs were therefore considered highly uncertain due to the impact of the survival benefit on the ICERs. The most favourable ICER was between $45,000 and $75,000 per extra QALY gained using the IPCW method and between $75,000 and $105,000 per extra QALY gained when calculated using the RPSFT method, but both were considered to be highly uncertain and likely to favour everolimus.

The sponsor in its Pre-Sub-Committee Response considered that the modelled OS gain using RPSFT of 5.6 months was reasonable because the ratio of 1.6 of PFS advantage to OS advantage (i.e. 5.6 months OS divided by 3.5 months PFS) is in agreement with the findings of Delea et al. (2009). The sponsor further reiterated in its Pre-PBAC response that the results of Delea et al. (2009) support the claim that the advantage in OS is more than the advantage in PFS. The PBAC was concerned that there may be differences in the way PFS is measured across the studies used in Delea, especially between earlier and later studies. Earlier studies generally had a stronger relationship between PFS and OS, which may partly relate to less crossover but may also relate to the measurement of progression in the later studies at earlier stages and with fewer clinical manifestations of progression. The PBAC noted that it was not clear that the evidence from this set of studies translates to this context where there is substantial cross over at 2 months following the first radiological assessment. The PBAC further noted that the linear regression analysis of PFS versus OS in Delea et al. (2009) includes the confidence limits but not the prediction bands. The prediction bands identify the minimum change in PFS required to predict a significant change in survival and also the range of benefit (rather than a point estimate). The possible range of improvement in overall survival could then be determined. However, the PBAC considered the key concern is that there are only limited data available for the construction of the placebo arm using either the IPCW or RPSFT methods due to the early and high cross over of patients to everolimus.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and a high and uncertain cost-effectiveness ratio.

The PBAC noted that the submission meets the criteria for an independent review.

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 will continue to work with the PBAC to resolve the issues identified in this re-submission.