

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Everolimus, tablet, 5 mg and 10 mg, Afinitor<sup>®</sup>

**Sponsor:** Novartis Pharmaceuticals Australia Pty Ltd

**Date of PBAC Consideration:** November 2009

### **1. Purpose of Application**

The submission sought an authority required PBS listing for the treatment of a patient with Stage IV clear cell variant renal cell carcinoma (RCC) after failure of sunitinib or sorafenib.

### **2. Background**

This drug has not previously been considered by the PBAC for this indication.

### **3. Registration Status**

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

Everolimus tablets 5 mg and 10 mg were TGA registered on 6 August 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

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.

#### Authority required (grandfather)

Treatment, as the sole PBS-subsidised therapy, of a patient with Stage IV clear cell variant renal cell carcinoma who was eligible under the above criteria and was receiving treatment with everolimus prior to (insert LISTING DATE).

#### NOTE:

Patients should continue everolimus treatment until the first occurrence of radiologically documented disease progression according to RECIST criteria.

*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. 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.

### **6. Comparator**

Appropriately, the submission nominated placebo for best supportive care as the main comparator as there are no PBS-subsidised second-line treatment alternatives upon disease progression after first-line treatment with sunitinib.

## 7. Clinical Trials

The submission presented one randomised trial, RECORD-1, comparing everolimus, 10 mg per day orally, with placebo in patients with Stage IV clear cell renal cell carcinoma with Karnofsky performance score of at least 70 and having demonstrated progression on or within six months of treatment with sunitinib or sorafenib. Crossover to everolimus for placebo patients was allowed after progression.

The trial published at the time of submission is shown in the table below. This publication used the second interim analysis data cut-off of 15 October 2007.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Motzer R, Escudier B, Oudard S, et al.	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial	Lancet 2008; 372(9637):449-56

The submission also presented unpublished updated data from a later cut-off (28 February 2008) on progression free survival and overall survival.

## 8. Results of Trials

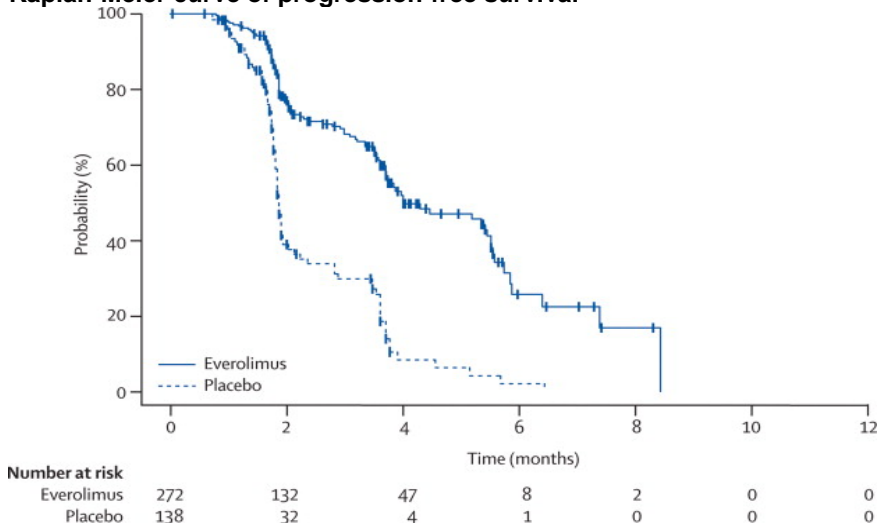
The results for the primary outcome, progression-free survival (PFS), are shown below.

### Progression-free survival (by independent review) as of 15 October 2007

Analysis	Result (95% CI)	Level of statistical significance needed
<b>Progression-free survival – 191 events</b>		
<b>Everolimus (n=272): 101 (37%) events – 85 progressions, 16 deaths</b>		
<b>Placebo (n=138): 90 (65%) events – 82 progressions, 8 deaths</b>		
Comparison of time-to-first event curves	2-sided stratified log rank test	P<0.0001
	CPH	HR = 0.30 (0.22, 0.40)
	Median progression-free survival Everolimus = 4.0 mo (3.7, 5.5) Placebo = 1.9 mo (1.8, 1.9)	P=0.0057
		NA

NA: not applicable, CPH: Cox Proportional Hazards.

### Kaplan-Meier curve of progression-free survival



The PBAC noted that the RECORD-1 trial showed a statistically significant benefit in PFS for everolimus compared with placebo although the magnitude of the gain was small. The hazard ratios and 95% CIs were similar when progression was determined by the investigator and when determined across various pre-planned subgroups (prior treatment, age, gender and geographic region).

At the time of the 15 October 2007 analysis, median overall survival had not been reached for the everolimus group and was 8.8 months for the placebo group.

The PBAC noted that there was no statistically significant difference between everolimus and placebo in overall survival from the published data (HR=0.83, 95% CI: 0.50, 1.37, p=0.23) or from the data included from the later cut-off.

The PBAC considered that the results for the secondary outcomes of Karnofsky performance status, physical function, and QOL (quality of life) scores showed no statistically significant differences in QOL and performance status between everolimus and placebo treated patients. However, these results are difficult to interpret because of the substantial crossover of placebo patients to everolimus treatment.

Everolimus has significant on-treatment toxicity compared to placebo, including increased risk of serious infection, non-infectious pneumonitis, dyspnea, stomatitis, hyperglycaemia, anaemia, lymphopenia as well as neurotoxicity.

*For PBAC's comments on these results, see Recommendation and Reasons.*

## **9. Clinical Claim**

The submission described everolimus as being superior in terms of comparative effectiveness in PFS and inferior in terms of comparative safety over placebo.

The PBAC considered that, based on the supporting data, the claim of superior effectiveness is reasonable for progression-free survival (PFS) but the difference in median PFS is small. However, no benefit was demonstrated in overall survival or quality-of-life.

## **10. Economic Analysis**

The submission presented a stepped economic evaluation using a decision-analytic Markov model comparing everolimus and placebo. It consisted of three health states, stable disease, progressive disease, and death, and had a 3-year horizon.

The model was most sensitive to assumptions regarding mortality with uncertainties arising because of the wide confidence interval around the survival estimate derived from the inverse censoring probability weighted (ICPW) model and differences in risk of death after progression in assumed differences in risks of death from non-progressed and progressed disease.

The PBAC noted that using the survival hazard ratio from the trial, the incremental cost per QALY gained increased the base case from being in the range of \$45,000 – \$75,000 to in the range of \$75,000 – 105,000. Using the upper 95% confidence limit from the submission's

IPCW analysis further increased the incremental cost per QALY gained to be in the range of \$105,000 – \$200,000.

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

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

The financial cost per year to the PBS was estimated to be in the range of \$10 – \$30 million per year in Year 5.

### **12. Recommendation and Reasons**

The PBAC noted that when sorafenib is used as a first line agent, sorafenib failed to show benefit in terms of progression free survival (PFS) or overall survival but when used as a second-line agent after failure of a cytokine showed a PFS of about 2.7 months. Therefore, the study population for everolimus was a combination of patients who had failed tyrosine kinase inhibitors (TKIs) (sunitinib) and patients who had never been exposed to an effective TKI (sorafenib). Given that sorafenib has failed to show any benefit as a first line agent in RCC, the PBAC considered that this may have influenced the benefit observed for everolimus.

The PBAC considered that there is a clinical need for options for people who have failed sunitinib. However, sorafenib is not available in Australia and therefore the requested PBS listing is not entirely consistent with the population who will use the drug. The PBAC considered that any future restriction should specify use after disease progression on sunitinib rather than failure of treatment as this implied resistance to treatment and there was no way of measuring this as yet. In addition, the restriction should also specify that everolimus should not be used after failure of temsirolimus, both being mTOR inhibitors.

The PBAC noted that the RECORD-1 trial showed a statistically significant benefit in PFS for everolimus compared with placebo although the magnitude of the gain was small. The PBAC noted that there was no statistically significant difference between everolimus and placebo in overall survival. The PBAC considered that the results indicated that radiological progression is a poor predictor of survival in this context, particularly since the difference was small. If disease free survival were a good marker of overall survival then there should be some survival signal, despite crossover to everolimus, but the benefit is small. By comparing disease free survival and survival curves it appears that factors other than disease free survival may be important for predicting overall survival.

The PBAC noted that everolimus is also associated with serious on-treatment toxicity such as non-infectious pneumonitis, dyspnea, stomatitis, hyperglycaemia, anaemia, and lymphopenia. However, only serious adverse events occurring at a rate of at least 2%, dyspnoea and pneumonitis, were included in the model. The PBAC considered that the results for Karnofsky performance status, physical function, and QOL (quality of life) scores showed no statistically significant differences in QOL and performance status between everolimus and placebo treated patients. However, these results are difficult to interpret because of the substantial crossover of placebo patients to everolimus treatment.

Therefore, based on the supporting data, the claim of superior effectiveness is reasonable for progression-free survival (PFS) but the difference in median PFS is small. However, no benefit was demonstrated in overall survival or quality-of-life.

The PBAC considered that the main area of uncertainty was in the estimation of survival within study with inverse censoring probability weighted (ICPW) method relative to conventional methods. The PBAC noted that the ICPW technique attempts to adjust for extreme confounding with crossover by re-weighting individuals in the placebo arm. Individuals with low probability of crossover are weighted almost the same as patients in the treatment arm, while patients with high probability of crossover are weighted close to 0. In addition the ICPW method has been classed in the literature as ‘causal’ or ‘counterfactual’ in using group evidence to predicting what would have happened for individuals who were censored.

The PBAC noted that the ICPW model generated a hazard ratio (HR) estimate which continued to be applied in the model from 12 to 36 months. The PBAC considered that there is an overestimation in benefits with extrapolation of treatment effects for progression and survival beyond 12 months to 3 years and that the HR was uncertain.

The PBAC agreed that there is an overall lack of supporting evidence for extrapolation of within study estimated incremental difference in median time of progression free survival to a modelled result over 3 years.

The PBAC noted that using the survival hazard ratio from the trial, the incremental cost per QALY gained increased the base case from being in the range of \$45,000 – \$75,000 to in the range of \$75,000 – 105,000 . Using the upper 95% confidence limit from the submission’s IPCW analysis further increased the incremental cost per QALY gained to be in the range of \$105,000 – \$200,000.

The PBAC considered that although there was a clinical need for everolimus and trial-based evidence of improved PFS, the magnitude of that clinical benefit is highly uncertain in terms of overall survival. The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and a high and uncertain cost-effectiveness ratio.

***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 Sponsors will continue to work with PBAC to resolve the issues identified in this submission.