

## 7.13 EVEROLIMUS, tablets, 5 mg and 10 mg, Afinitor<sup>®</sup>, Novartis Pharmaceuticals Australia Pty Ltd

### 1 Purpose of Application

- 1.1 The minor re-submission sought a General Schedule Authority Required listing for the treatment of Stage IV clear cell variant renal cell carcinoma (RCC) after progression on sunitinib.

### 2 Requested listing

#### 2.1 Authority required

Stage IV clear cell variant renal cell carcinoma (RCC)

Treatment phase: Initial treatment

The Clinical criteria is:

Patient must have failed treatment with sunitinib

AND the Clinical criteria is

Progressive disease is defined by the Response Evaluation Criteria in Solid Tumours (RECIST)

OR

Toxicity that is sunitinib related and necessitates permanent cessation of sunitinib.

AND the Clinical criteria is

Patient must have a WHO performance status of 2 or less.

AND the Clinical criteria is

The treatment must be the sole PBS-subsidised mTOR inhibitor for this condition

#### Authority required

Stage IV clear cell variant renal cell carcinoma (RCC)

Treatment phase: Continuing treatment beyond 3 months

The Clinical criteria is:

Patient must have previously been issued with an Authority prescription for everolimus

AND the Clinical criteria is

Patient must have stable or responding disease according to RECIST

AND the Clinical criteria is

The treatment must be the sole PBS-subsidised mTOR inhibitor for this condition.

- 2.2 The PBAC noted that both sunitinib and pazopanib are currently available on the PBS for the treatment of stage IV clear cell variant RCC. Under the proposed restriction for everolimus, patients who have failed prior treatment with pazopanib would not be eligible to receive PBS-subsidised everolimus. The PBAC considered that it was appropriate that patients who have failed pazopanib should be able to access everolimus and recommended that the restriction be amended to allow use in patients who have progressive disease following treatment with a tyrosine kinase inhibitor (TKI).

- 2.3 The PBAC considered the requested maximum quantity was appropriate. The PBAC recommended that the number of repeats should be two for initial treatment and five

for continuing treatment. The PBAC noted that this would provide the same total duration of therapy as is available on the PBS for sunitinib and pazopanib.

- 2.4 The PBAC considered that it was appropriate that the restriction should allow use of everolimus in patients who develop intolerance to first-line TKI therapy of a severity necessitating permanent treatment withdrawal.

### **3 Background**

- 3.1 Everolimus is TGA registered for the following indications:

- 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.
- 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 advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.
- For the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), who require therapeutic intervention but are not candidates for curative surgical resection.
- For the treatment of patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.

- 3.2 This was the fifth submission requesting PBS listing for everolimus for clear cell variant RCC. Most recently, a minor-resubmission was rejected at the November 2011 PBAC meeting on the basis of a high and uncertain cost-effectiveness ratio.

### **4 Clinical place for the proposed therapy**

- 4.1 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.

- 4.2 Everolimus would be a new treatment option for patients with advanced RCC who have failed prior therapy with a TKI.

### **5 Comparator**

- 5.1 The PBAC has previously considered best supportive care (BSC) to be the appropriate comparator.

## 6 PBAC consideration of the evidence

### Consumer comments

6.1 The PBAC acknowledged that a clinical need exists for treatment of this condition, noting that no second line treatments are currently available on the PBS. The PBAC welcomed and noted the input received from individuals (2) and health care professionals (4) via the consumer comments facility on the PBS website in support of the re-submission. The comments received made reference to the clinical need for a subsidised treatment in the second-line setting.

### Clinical trials

6.2 No new clinical data were presented in this re-submission.

### Comparative effectiveness

6.3 The results of the RECORD-1 trial had been previously presented and are summarised in the table and figure below.

#### Progression free and overall survival in the RECORD-1 trial

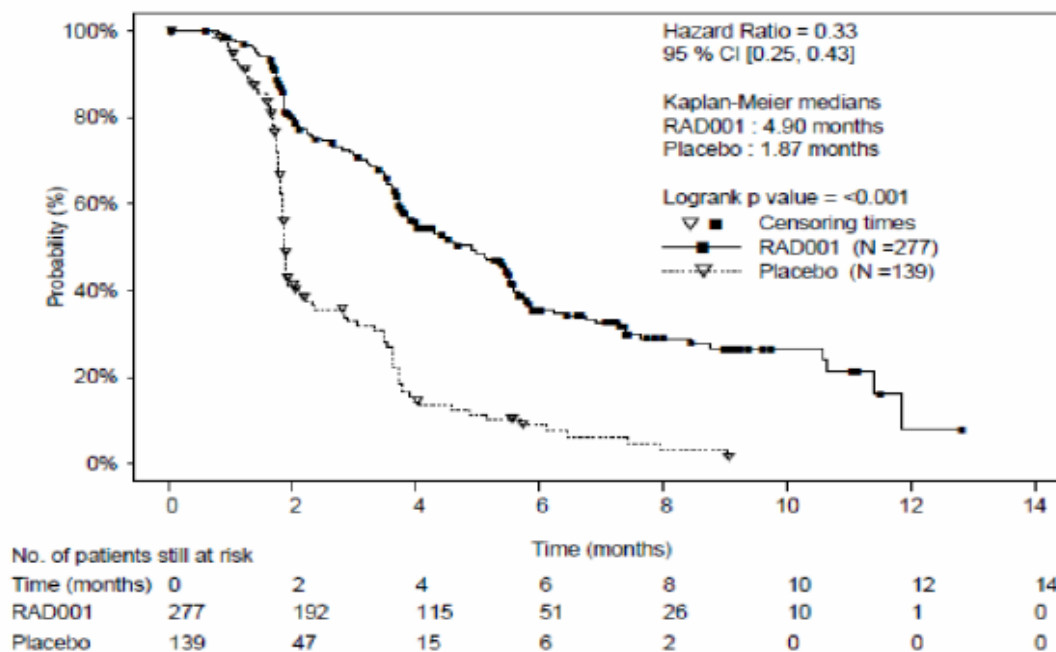
Trial ID	Number (%) with event		Hazard ratio <sup>a</sup> (95% CI)	Log rank p value <sup>b</sup>
	Everolimus N=277	Placebo N=139		
RECORD-1				
PFS	155 (56.0)	111 (79.9)	0.33 (0.25, 0.43)	<0.001
OS	85 (30.7)	48 (34.5)	0.82 (0.57, 1.17)	0.137

a Cox model; b One-sided stratified log-rank test

Source: CSR Efficacy Update, p 7; CSR Efficacy Update p 11

CI = confidence interval; N = total number of patients in group; PFS = progression free survival

#### Kaplan-Meier progression free survival curves.



CI= confidence interval; N = total number of patients in group; RAD001 = everolimus

- 6.4 The PBAC recalled that the main uncertainty in November 2011 was whether there was a survival gain associated 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. In November 2011, the PBAC considered that for the ICER to be acceptable, a further price reduction would be necessary, with a risk share agreement and a cap to account for use beyond progression.
- 6.5 The PBAC remained of the opinion that the best estimate of survival gain was between 3 months (based on the trial based incremental PFS) and 4.8 months (based on estimated OS using Rank-Preserving Structural Failure Time (RPSFT)).

**Comparative harms**

- 6.6 The PBAC recalled that it had previously considered everolimus to be inferior to placebo in terms of safety.

**Clinical claim**

- 6.7 The re-submission did not alter its November 2011 claim that everolimus has superior efficacy and inferior safety in mRCC compared with placebo.

**Economic analysis**

- 6.8 The re-submission presented an updated cost-effectiveness model. The model was the same as that presented in the November 2011 re-submission, with the exception that the effective price was further reduced [REDACTED]

- 6.9 The PBAC noted that the ESC Advice from November 2011 highlighted an error with the model with the Weibull overall survival curves for which the sponsor proposed a correction. The correction had not been incorporated into the model in the current re-submission. The model was re-run using the corrected 'A' parameters. Results are presented in the table below.

	'A' Parameter in model	ICER (\$/QALY)
<b>Minor submission's model (DPMQ of 10mg= [REDACTED])</b>		
3 months	[REDACTED]	[REDACTED]
4.8 months	[REDACTED]	[REDACTED]
<b>Changes using values for the 'A' parameter in ESC advice (DPMQ of 10mg= [REDACTED])</b>		
3 months	[REDACTED]	[REDACTED]
4.8 months	[REDACTED]	[REDACTED]

- 6.10 The PBAC noted the corrected economic analysis produced ICERs of between a range of \$75,000 and \$105,000/QALY and between a range of \$45,000 and \$75,000/QALY using survival gains of 3 months and 4.8 months, respectively. The PBAC noted the uncertainty in relation to the survival gain. As noted above, the committee considered that the survival gain was likely to be between the estimates of 3 and 4.8 months and therefore the ICER was likely to be lower than between a range of \$75,000 and \$105,000/QALY, but higher than between a range of \$45,000 and \$75,000/QALY. Given the clinical need for treatments in this population of patients, the PBAC therefore considered that at the price proposed in re-submission,

everolimus was acceptably cost-effective. The PBAC recalled that the ICER at which everolimus was recommended for listing in advanced breast cancer was also within this range \$45,000 to \$75,000/QALY).

**Estimated PBS usage & financial implications**

6.11 The re-submission presented updated estimates of PBS usage and financial implications. These are presented in the table below.

**Estimates of usage and net cost to PBS for the drug at the published and effective prices**

	Year 1 2014	Year 2 2015	Year 3 2016	Year 4 2015	Year 5 2016
Number of patients	████	████	████	████	████
Number of prescriptions (10 mg tablets)	████	████	████	████	████
Net cost to Government- Published price	████████	████████	████████	████████	████████
Net cost to Government- Effective price	████████	████████	████████	████████	████████

Source: Table 5, page 7 of the re-submission.

6.12 The PBAC considered the submission’s estimates overestimated the likely number of patients who would receive treatment with everolimus for RCC after failure of TKI therapy.

6.13 The PBAC recalled its November 2013 consideration of axitinib and sorafenib for treatment of RCC in patients with disease progression following TKI therapy. The PBAC agreed with the DUSC advice from November 2013 that estimates based on the actual number of patients who are treated with PBS subsidised sunitinib or pazopanib provide more robust estimates of use within the proposed restriction.

6.14 The PBAC noted that the sponsor had indicated a willingness to enter into a risk-sharing arrangement and requested a special pricing arrangement. The PBAC recommended that estimates of patient numbers based on the actual number of patients treated with PBS subsidised sunitinib or pazopanib for RCC in the first-line setting should form the basis of a risk-sharing arrangement, to be negotiated between the Department and the sponsor.

**7 PBAC Outcome**

7.1 The PBAC recommended extending the current PBS Authority required listing for everolimus to include initial and continuing treatment of stage IV clear cell variant RCC in patients who have disease progression following treatment with a PBS-subsidised tyrosine kinase inhibitor.

7.2 The PBAC was satisfied that everolimus provides, for some patients, a significant improvement in efficacy over best supportive care.

7.3 As previously, the PBAC agreed that BSC was the appropriate comparator.

7.4 The PBAC’s recommendation for listing was based on, among other matters, its assessment that the survival gain was likely to be between the estimates of 3 and 4.8 months and therefore the ICER was likely to be lower than between a range of \$75,000 to \$105,000/QALY, but higher than between a range of \$45,000 to

\$75,000/QALY. Given the clinical need for treatments in this population of patients, the PBAC therefore considered that at the price proposed in re-submission, everolimus was acceptably cost-effective. The PBAC therefore considered that at the price proposed in re-submission, everolimus was acceptably cost-effective. The PBAC recalled that the ICER at which everolimus was recommended for listing in advanced breast cancer was also within this range (\$45,000 to \$75,000/QALY), but the estimate of survival for second line renal cancer is more uncertain.

- 7.5 The PBAC also requested, should additional data about the survival benefit of everolimus become available in the future, the sponsor provide the data to the PBAC to provide more certainty about the overall survival benefit.
- 7.6 With no new clinical safety data presented in the re-submission, the PBAC had no reason to alter its previous acceptance that everolimus is inferior to placebo in terms of safety.
- 7.7 The PBAC did not accept the re-submission's revised estimates of usage and financial implications. The PBAC agreed with the DUSC advice from the November 2013 consideration of axitinib and sorafenib for treatment of Stage IV RCC in patients with disease progression following first-line TKI therapy: that estimates based on the actual number of patients who are treated with PBS subsidised sunitinib or pazopanib provide more robust estimates of use within the proposed restriction. The PBAC recommended that these estimates should be used to determine usage caps in a risk-sharing arrangement to be negotiated between the Department and the sponsor.
- 7.8 Advice to the Minister under subsection 101(3BA) of the *National Health Act*  
In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised that it is of the opinion that, on the basis of the material available to it at its March 2014 meeting, everolimus should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).
- 7.9 The PBAC advised that everolimus is not suitable for inclusion in the list of medicines for prescribing by nurse practitioners, nothing that chemotherapy agents are currently considered out of scope for prescribing by nurse practitioners.
- 7.10 The Safety Net 20 Day Rule should not apply.

**Outcome:**

Recommended

**8 Recommended listing**

8.1 Extend the existing listing for everolimus to include the following:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
EVEROLIMUS				
Tablet 5 mg	30	2	Afinitor	NV
Tablet 10 mg	30	2	Afinitor	NV

<b>Severity:</b>	Stage IV
<b>Indication:</b>	clear cell variant renal cell carcinoma (RCC)
<b>Treatment Phase:</b>	Initial treatment
<b>Restriction:</b>	Authority Required
<b>Clinical criteria:</b>	<p>Patient must have progressive disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less.</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
<b>Prescriber instructions:</b>	Patients who have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised everolimus.
<b>Prescriber instructions:</b>	Patients who have progressive disease with everolimus are no longer eligible for PBS-subsidised everolimus.
<b>Administrative Advice:</b>	<u>NOTE:</u> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b>	<u>NOTE:</u> No increase in the maximum number of repeats may be authorised.

<b>Administrative Advice:</b>	<b>NOTE:</b> Response Evaluation Criteria in Solid Tumours (RECIST) is 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.
<b>Administrative Advice:</b>	<b>NOTE:</b> Special Pricing Arrangements apply.

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

<b>Severity:</b>	Stage IV
<b>Indication:</b>	clear cell variant renal cell carcinoma
<b>Treatment Phase:</b>	Continuing treatment beyond 3 months
<b>Restriction:</b>	Authority Required
<b>Clinical criteria:</b>	Patient must have previously been issued with an authority prescription for this drug for this condition  AND  Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)  AND  The treatment must be the sole PBS-subsidised therapy for this condition.
<b>Prescriber instructions:</b>	Patients who have progressive disease with everolimus are no longer eligible for PBS-subsidised everolimus.
<b>Administrative Advice:</b>	<b>NOTE:</b> No increase in the maximum quantity or number of units may be authorised.
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<b>Administrative Advice:</b>	<b>NOTE:</b> Special Pricing Arrangements apply.

### **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.

### **Sponsor's Comment**

Novartis welcomes the PBAC decision and look forward to the PBS listing of everolimus for patients with renal cell carcinoma.