# 7.12 EVEROLIMUS, tablets, 5 mg and 10 mg, Afinitor®, 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 metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET).

## 2 Requested listing

2.1 **Authority required**
Metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET).

Treatment phase: Initial treatment

The clinical criteria is:
Patient must be symptomatic (despite somatostatin analogues); OR
Patient must have disease progression,

AND the clinical criteria is:
The treatment must be as monotherapy.

Disease progression must be documented in the patient's medical records.

Note:
No increase in the maximum quantity or number of units may be authorised.

Note:
No increase in the maximum number of repeats may be authorised.

**Authority required**
Metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET).

Treatment phase: Continuing treatment

The clinical criteria is:
Patient must have previously been issued with an authority prescription for everolimus,

AND the clinical criteria is:
Patient must not have progressive disease,

AND the clinical criteria is:
The treatment must be as monotherapy.

Note:
Patients who have progressive disease with everolimus are no longer eligible for PBS-subsidised everolimus.

Note:
No increase in the maximum quantity or number of units may be authorised.

Note:
No increase in the maximum number of repeats may be authorised.

2.2 The PBAC noted that the requested listing was consistent with the current PBS listing for sunitinib for pNET, and limited use to patients with well differentiated tumours only.

2.3 The PBAC considered that there was the possibility of sequential use of everolimus and sunitinib. No data were presented to the PBAC supporting clinical efficacy and cost-effectiveness in this setting. The PBAC noted the sponsor's argument in its pre-PBAC response that recent listings for abiraterone and cabazitaxel for the treatment of metastatic castration-resistant prostate cancer do not include criteria preventing sequential use of these medicines. The sponsor stated that as for mCRPC, there is an unmet clinical need for patients with pNETs due to the lack of effective therapies in this area.

2.4 The PBAC considered that until data are presented to support the efficacy and cost-effectiveness of the sequential use of everolimus and sunitinib, it was appropriate that the restrictions for these agents include criteria to prevent such use. However, the PBAC agreed that patients who develop intolerance/toxicity to one agent of a severity necessitating permanent treatment withdrawal should be permitted to receive the other agent.

## 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 The PBAC had previously considered a major submission requesting PBS listing of everolimus for treatment of pNET in November 2012.

3.3 The PBAC rejected the submission on the basis of an inappropriate comparator (sunitinib, which was not PBS listed at the time) and the resultant invalid cost-minimisation analysis.

3.4 Sunitinib was subsequently recommended for listing by the PBAC at its Special meeting in August 2013 on the basis of acceptable cost-effectiveness. Listing was effective from 1 December 2013.

## 4 Clinical place for the proposed therapy

4.1 Unresectable or metastatic pancreatic NETs are rare cancers with a poor prognosis.

4.2 Sunitinib is currently the only PBS-listed treatment for unresectable or metastatic pNET. If recommended for listing, everolimus would be an alternative PBS-subsidised treatment to sunitinib for this condition.

## 5 Comparator

5.1 The re-submission nominated sunitinib as the comparator. This was considered appropriate by the PBAC.

## 6 PBAC consideration of the evidence

### *Consumer comments and sponsor hearing*

6.1 The PBAC noted consumer comments from 22 individual and three organisations (the Medical Oncology Group of Australia (MOGA), the Unicorn Foundation Australia and Rare Cancers Australia). The PBAC noted that the consumer comments highlighted the benefits of everolimus for quality of life in this rare condition, especially with respect to alleviation of symptoms and slowed tumour growth.

6.2 The sponsor did not request a hearing for this item.

### *Clinical trials*

6.1 No new clinical data were presented in the re-submission compared to the November 2012 major submission. The re-submission re-presented a summary of the results of the indirect comparison of two phase III randomised controlled trials comparing everolimus 10 mg/day in 410 patients with moderately/well differentiated pNETs (RADIANT-3) with sunitinib 37.5 mg/day in 171 patients with well differentiated pNETs (Study A618-1111), with the common comparator, placebo.

### *Comparative effectiveness*

6.2 Results of the indirect comparison are presented in the table below.

**Indirect comparison of progression free survival and overall survival.**

| Trial ID | Comparison | HR (95% CI) | Indirect comparison Everolimus vs Sunitinib (95% CI) |
|---|---|---|---|
| **Progression free survival** | | | |
| RADIANT-3 | Everolimus vs Placebo | 0.35 (0.27, 0.45) | 0.83 (0.50, 1.40) |
| A618-1111 | Sunitinib vs Placebo | 0.42 (0.26, 0.66) | |
| **Overall survival[a]** | | | |
| RADIANT-3 | Everolimus vs Placebo | 0.89 (0.64, 1.23) | 1.21 (0.69, 2.12) |
| A618-1111 | Sunitinib vs Placebo | 0.74 (0.47, 1.17) | |

Abbreviations: CI, confidence interval; HR, hazard ratio.
Notes: A Second data cut-off and ITT analysis used for both studies.
Source: Table 23 Section B, p57 of the November 2012 submission.

6.3 The PBAC recalled that it did not accept that everolimus was non-inferior to sunitinib in terms of clinical effectiveness in its consideration of the November 2012 submission. The PBAC considered the claim of non-inferiority to be uncertain due to limitations regarding exchangeability and possible biases associated with early termination of Trial A618-1111 and high crossover for assessment of overall survival.

6.4 The PBAC noted the results of a recently published matching-adjusted indirect comparison by Signorovitch et al[1] which showed that compared to sunitinib, everolimus was associated with similar progression-free survival (PFS) and overall survival (OS). The matching-adjusted indirect comparison was based on a weighted Cox proportional hazards model and weighted Kaplan-Meier estimates, which were used to compare OS between the everolimus arm in RADIAN-3 and the placebo arm in A618-1111. Thus, the placebo arm in Trial A618-1111 was treated as an external control population. The results are presented in the table below.

| | Pre-matching | | | Post Matching | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-Value | HR | 95% CI | P-Value |
| Progression-Free Survival | | | | | | |
| Everolimus vs A618 Placebo | 0.38 | 0.29-0.49 | <0.001 | 0.35 | 0.24-0.52 | <0.001 |
| Sunitinib vs A618 Placebo | 0.42 | 0.26-0.66 | <0.001 | 0.42 | 0.26-0.66 | <0.001 |
| **Everolimus vs Sunitinib** | 0.9 | 0.53-1.53 | 0.695 | **0.84** | 0.46-1.53 | 0.578 |
| Overall Survival | | | | | | |
| Everolimus vs A618 Placebo | 0.53 | 0.35-0.78 | 0.002 | 0.61 | 0.38-0.98 | 0.042 |
| **Everolimus vs Sunitinib** | 0.69 | 0.46-1.05 | 0.087 | **0.81** | 0.49-1.31 | 0.383 |

Source: Signorovitch et al. Experimental Haematology & Oncology 2013; 2:32

6.5 The PBAC considered that the results of the matching-adjusted indirect comparison supported the conclusion that everolimus is non-inferior to sunitinib in terms of clinical effectiveness.

***Comparative harms***

6.6 The table below presents the indirect comparison of adverse events. The same table was provided by the sponsor in its pre-Sub-Committee response (PSCR) for the November 2012 submission.

[1] Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: a matching-adjusted indirect comparison. *Experimental Hematology & Oncology* 2013, 2:32 doi:10.1186/2162-3619-2-32

**Indirect comparison of Adverse Events- Revised**

| Trial ID | Comparison | Active Treatment n/N (%) | Placebo n/N (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) |
|---|---|---|---|---|---|---|
| **At least one AE** | | | | | | |
| RADIANT-3 | Everolimus vs Placebo | 202/204 (99.0%) | 198/203 (97.5%) | 2.6 (0.5, 13.3) | 1.02 (0.99, 1.04) | 1.5% (-1.0%, 4.0%) |
| A618-1111 | Sunitinib vs Placebo | 82/83 (98.8%) | 78/82 (95.1%) | 4.2 (0.5, 38.5) | 1.04 (0.98, 1.10) | 3.7% (-1.5%, 8.9%) |
| Indirect comparison: Everolimus vs Sunitinib | | | | 0.6 (0.0, 9.6) | 0.98 (0.92, 1.04) | -2.2% (-8.0%, 3.6%) |
| **At least one Grade 3 or 4 AE** | | | | | | |
| RADIANT-3 | Everolimus vs Placebo | 122/204 (59.8%) | 79/203 (38.9%) | 2.3 (1.6, 3.5) | 1.54 (1.25, 1.88) | 20.9% (11.4%, 30.4%) |
| A618-1111 | Sunitinib vs Placebo | 41/83 (49.4%) | 36/82 (43.9%) | 1.2 (0.7, 2.3) | 1.13 (0.81, 1.56) | 5.5% (-9.7%, 20.7%) |
| Indirect comparison: Everolimus vs Sunitinib | | | | 1.9 (0.9,3.9) | 1.37 (0.93, 2.01) | 15.4% (-2.5%, 33.3%) |
| **At least one serious AE** | | | | | | |
| RADIANT-3 | Everolimus vs Placebo | 82/204 (40.2%) | 50/203 (24.6%) | 2.1 (1.3, 3.1) | 1.63 (1.22, 2.19) | 15.6% (6.6%, 24.5%) |
| A618-1111 | Sunitinib vs Placebo | 22/83 (26.5%) | 34/82 (41.5%) | 0.5 (0.3, 1.0) | 0.64 (0.41, 0.99) | -15.0% (-29.2%, -0.7%) |
| Indirect comparison: Everolimus vs Sunitinib | | | | 4.0 (1.8, 8.8) | 2.55 (1.50, 4.34) | 30.5% (13.7%, 47.4%) |
| **On treatment deaths (within 28 days of end of double blind treatment)** | | | | | | |
| RADIANT-3 | Everolimus vs Placebo | 12/204 (5.9%) | 4/203 (2%) | 3.1 (1.0, 9.8) | 2.99 (0.98, 9.10) | 3.9% (0.2%, 7.7%) |
| A618-1111 | Sunitinib vs Placebo | 5/83 (6.0%) | 9/82 (11.0%) | 0.5 (0.2, 1.6) | 0.55 (0.19, 1.57) | -5.0% (-13.4%, 3.5%) |
| Indirect comparison: Everolimus vs Sunitinib | | | | 6.0 (1.2, 30.1) | 5.44 (1.18, 25.15) | 8.9% (-0.4%, 18.1%) |

Abbreviations: AE, adverse event; CI, confidence interval; OR, odds ratio; RD, risk difference; RR, relative risk

6.7 The PBAC recalled that it had previously considered that everolimus and sunitinib have different toxicities. In its consideration of the November 2012 submission, the PBAC considered there was insufficient evidence to accept the claim that everolimus is non-inferior to sunitinib in terms of comparative safety and may in fact be inferior.

6.8 The PBAC noted the re-submission's pre-PBAC response (p2) where the sponsor maintained that that RADIANT-3 and A618-1111 are not directly comparable in terms of safety reporting due to the substantially longer exposure to everolimus than sunitinib (8.7 versus 4.6 months), and that the direction of bias is in favour of sunitinib.

6.9 The PBAC noted the input received from the Medical Oncology Group of Australia in relation to the re-submission, where everolimus was described as being generally well tolerated, though grade 1 or 2 toxicity is common. Metabolic abnormalities were also reported to be common. Regular monitoring is recommended, and medical management usually sufficient. Infection and non-infective pneumonitis were highlighted as potentially more severe toxicities, which may require discontinuation of therapy.

### *Clinical claim*

6.10 The re-submission described everolimus as non-inferior to sunitinib in terms of clinical effectiveness for the treatment of patients with advanced pNET, with a different, but manageable, safety profile.

6.11 The PBAC accepted the re-submission's clinical claim.

### *Economic analysis*

6.12 The re-submission presented a cost-minimisation analysis versus sunitinib based on the claim of non-inferiority. The PBAC agreed that a cost-minimisation approach was appropriate.

6.13 The PBAC recommended that the equi-effective doses for the cost-minimisation analysis should be everolimus 8.59 mg daily until progression or high toxicity and sunitinib 34.24 mg daily until progression or high toxicity. The doses are based on clinical trial evidence from RADIANT-3 and A618-1111.

### *Estimated PBS usage & financial implications*

6.14 The re-submission presented revised estimates of PBS usage and financial implications. Compared to the November 2012 submission, the re-submission increased the percentage of NET patients with pNET from 3.5% to 6.5% using the same reference paper (Luke et al. 2010), and decreased the proportion of metastatic/unresectable pNET cases with well-differentiated tumour from 90% to 75% based on clinician input. This resulted in an increase in the likely number of patients treated from less than 10,000 in November 2012 to less than 10,000.

6.15 The PBAC did not accept the re-submission's estimates of usage and cost. The PBAC considered that it was not appropriate to use the percentage of pNET incidence in the calculation of prevalence as pNET is associated with much poorer survival compared with other NETs.

6.16 The PBAC considered that the estimate of the number of patients treated should be consistent with that previously accepted for sunitinib.

6.17 The re-submission acknowledged the existence of special pricing arrangements for sunitinib. The re-submission proposed that the effective price for sunitinib be applied to the equi-effective doses of everolimus, and everolimus be included as part of any risk-sharing arrangement involving sunitinib for pNET.

6.18 The PBAC recommended that a risk-sharing arrangement be negotiated so that everolimus and sunitinib for pNET share the same market, to minimise financial risk and allow monitoring of PBS medication use in this disease.

## 7 PBAC Outcome

7.1 The PBAC recommended extending the current PBS Authority required listing for everolimus to include initial and continuing treatment of metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET). Listing was recommended on a cost-minimisation basis with sunitinib using the trial-based equi-effective doses of everolimus 8.59 mg daily until progression or intolerance and sunitinib 34.24 mg daily until progression or intolerance.

7.2 Listing was recommended with a maximum quantity of 30 tablets with two repeats for initial treatment, and of 30 tablets with five repeats for continuing treatment.

7.3 The PBAC acknowledged that a high clinical need exists for treatments for metastatic pNET. The PBAC noted that currently, sunitinib is the only PBS-listed treatment available for this condition.

7.4 The PBAC considered that the requested restriction was appropriate, but recommended that a criterion be added to prevent sequential use of everolimus and sunitinib, given that no evidence had been presented to support the clinical efficacy and cost-effectiveness of everolimus in this setting. The PBAC also recommended that the same criterion be included in the current restriction for sunitinib for consistency. However, the PBAC recommended that patients who experience intolerance/toxicity to one agent of a severity necessitating permanent treatment withdrawal should be permitted to access PBS-subsidised treatment with the other agent.

7.5 The PBAC accepted that sunitinib was the appropriate comparator, being the treatment most likely to be replaced in clinical practice.

7.6 The PBAC noted that no new clinical data as presented in the re-submission compared to the November 2012 submission. The PBAC recalled that it did not accept that everolimus was non-inferior to sunitinib in terms of clinical effectiveness based on the indirect comparison presented in the November 2012 submission. However, the PBAC noted the results of a recently published matching-adjusted indirect comparison by Signorovitch et al which showed that compared to sunitinib, everolimus was associated with similar progression-free survival (PFS) and overall survival (OS). The PBAC considered that the results of this matching-adjusted indirect comparison supported the conclusion that everolimus is non-inferior to sunitinib in terms of clinical effectiveness.

7.7 No new toxicity data were presented in the re-submission. The PBAC recalled that it had previously considered everolimus and sunitinib have different toxicities.

7.8 Overall, the PBAC considered the re-submission's claim that everolimus is non-inferior to sunitinib in terms of clinical effectiveness for the treatment of patients with advanced pNET, with a different, but manageable, safety profile, was reasonable.

7.9 The PBAC did not accept the re-submissions estimates of usage and cost. The PBAC considered that it was not appropriate to use the percentage of pNET incidence in the calculation of prevalence as pNET is associated with much poorer survival compared with other NETs. The PBAC recommended that a risk-sharing arrangement be negotiated so that everolimus and sunitinib for pNET share the same market, to minimise financial risk and allow monitoring of PBS medication use in this disease.

7.10 The PBAC considered that everolimus for pNET is not suitable for prescribing for nurse practitioners.

7.11 The Safety Net 20 Day Rule should not apply.

7.12 Advice to the Minister under Section 101(3BA) of the *National Health Act 1953*
The PBAC advised that, under Section 101 (3BA) of the National Health Act,

everolimus should not be treated as interchangeable with any other drug on an individual patient basis.

**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 | №.of Rpts | Proprietary Name and Manufacturer | |
|---|---|---|---|---|
| EVEROLIMUS | | | | |
| everolimus 5 mg tablet, 30 | 30 | 2 | Afinitor | NV |
| everolimus 10 mg tablet, 30 | 30 | 2 | Afinitor | NV |

| | |
|---|---|
| **Severity** | Metastatic or unresectable, well-differentiated malignant |
| **Condition:** | pancreatic neuroendocrine tumour (pNET) |
| **Treatment Phase:** | Initial treatment |
| **Restriction:** | Authority Required |
| **Clinical criteria:** | Patient must be symptomatic (despite somatostatin analogues)<br><br>OR<br><br>Patient must have disease progression<br><br>AND<br><br>The treatment must be as monotherapy |
| **Prescriber Instructions:** | Disease progression must be documented in the patient's medical records. |
| **Prescriber Instructions:** | Patients who have developed progressive disease on sunitinib are not eligible to receive PBS-subsidised everolimus. |
| **Prescriber Instructions:** | Patients who have developed intolerance to sunitinib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised everolimus. |
| **Administrative Advice:** | No increase in the maximum quantity or number of units may be authorised. |
| **Administrative Advice:** | No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:** | Special Pricing Arrangements apply. |

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

| | |
|---|---|
| **Severity** | Metastatic or unresectable, well-differentiated malignant |
| **Condition:** | pancreatic neuroendocrine tumour (pNET) |
| **Treatment Phase:** | Continuing treatment |
| **Restriction:** | Authority Required |
| **Clinical criteria:** | Patient must have previously been issued with an authority prescription for this drug<br><br>AND<br><br>Patient must not have disease progression<br><br>AND<br><br>The treatment must be as monotherapy |
| **Prescriber Instructions:** | Patients who have progressive disease with this drug are no longer eligible for PBS-subsidised treatment this drug. |
| **Administrative Advice** | No increase in the maximum quantity or number of units may be authorised. |
| **Administrative Advice** | No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice** | 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 is working with the Department of Health to finalise the details for the PBS listing of everolimus in pNET.