PUBLIC SUMMARY DOCUMENT
Product: Everolimus, tablets, 5 mg and 10 mg, Afinitor®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission sought an Authority Required listing for the initial and continuing treatment of unresectable or metastatic, well or moderately differentiated pancreatic neuroendocrine tumour (pNET) in a patient who is symptomatic or has disease progression.

2. Background

This was the first time the PBAC had considered the listing of everolimus for pNET.

Everolimus is currently listed on the PBS for the prophylaxis of organ transplant rejection.

3. Registration Status

Everolimus is currently registered with the Therapeutic Goods Administration (TGA) for the following indications:

- Prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant;
- Treatment of advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib;
- Treatment of subependymal giant cell astrocytoma associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection; and
- Progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine of pancreatic origin.

4. Listing Requested and PBAC's View

Authority required

Initial treatment of unresectable or metastatic, well or moderately differentiated pancreatic neuroendocrine tumour in a patient who is symptomatic (despite somatostatin analogues) or has documented disease progression.

Continuing treatment of patients with unresectable or metastatic, well or moderately differentiated pancreatic neuroendocrine tumour who have previously been issued with a PBS authority for everolimus and who do not have progressive disease.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

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

Treatment typically involves the use of somatostatin analogues (SSAs) supplemented by a range of other therapies.

Other therapies used to treat advanced pNETs include liver-directed therapies: selective internal radiation therapy (SIRT) and trans-catheter arterial chemo-embolisation (TACE); biological therapies: interferon and sunitinib; and chemotherapy. The submission stated that

based on expert opinion all therapies (SIRT/TACE, biologicals and chemotherapy) would be used in all patients. Patients cycle through the treatments and the sequence is varied according to patient characteristics and availability (access) of treatment.

Currently there are no targeted therapies on the PBS specifically for the treatment of advanced, metastatic, unresectable pNETs. The submission assumed that once available, everolimus would substitute for sunitinib.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated sunitinib as the comparator.

The PBAC did not agree that sunitinib was the appropriate comparator. The PBAC recalled from its July 2012 meeting that sunitinib was not recommended as cost-effective for this indication. The PBAC considered that a comparison with best supportive care (including symptomatic treatment with somatostatin analogues) is currently the most relevant comparator to inform the cost effectiveness of everolimus on the PBS, in particular for patients with well or moderately-differentiated tumours.

7. Clinical Trials

The submission presented an 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. In RADIANT-3, 72.8% of patients initially randomised to placebo crossed over to treatment at progression, and after early termination of Trial A618-1111, 69.4% of placebo patients (both progressed and non-progressed) crossed over to active treatment.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
RADIANT-3		
Chambers J et al.	Phase-3 randomized trial of everolimus (RAD001) vs. placebo in advanced pancreatic NET (RADIANT-3).	*Regulatory Peptides* (2010); 164(1): 6-7.
De Vries E et al.	Effect of everolimus treatment on chromogranin A, neuron-specific enolase, gastrin, and glucagon levels in patients with advanced pancreatic neuroendocrine tumors (pNET): Phase III RADIANT-3 study results.	*Journal of Clinical Oncology* (2011); 29(15).
Hobday T J et al.	Analysis of progression-free survival (PFS) by prior chemotherapy use and updated safety in radiant-3: A randomized, double-blind, placebo-controlled, multicenter, phase III trial of everolimus in patients with advanced low- or intermediate-grade pancreatic neuroendocrine tumors (PNET).	*Pancreas* (2012); 41(2): 345.
Hobday T J et al.	Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Multivariate analysis of	*Journal of Clinical Oncology* (2011);

Trial ID/ First author	Protocol title/ Publication title	Publication citation
	progression-free survival from the RADIANT-3 trial.	29(15).
Horsch D et al.	A randomized, double-blind, placebo-controlled, multicenter phase iii trial of everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET) (RADIANT-3): Updated safety results.	*Endocrine Reviews* (2011); 32(3).
Ito T et al.	Everolimus versus placebo in Japanese patients with advanced pancreatic neuroendocrine tumors (pNET): Japanese subgroup analysis of RADIANT-3.	*Journal of Clinical Oncology* (2011); 29(4).
Lombard-Bohas C et al.	Updated survival and safety data from radiant-3 - A randomized, double-blind, placebo-controlled, multicenter, phase III trial of everolimus in patients with advanced pancreatic neuroendocrine tumours (pNET).	*European Journal of Cancer* (2011); 47: S459.
Oberg K et al.	Role of chromogranin a and neuron-specific enolase biomarkers in progression-free survival (PFS) with everolimus (EVE) versus placebo (PB) in patients with advanced pancreatic neuroendocrine tumors (pNET): Phase III radiant-3 results.	*Neuroendocrinology* (2011); 94: 37.
Okusaka T et al.	Efficacy and safety of everolimus in Japanese patients with advanced pancreatic neuroendocrine tumors (pNET): Japanese subgroup analysis of radiant-3.	*Neuroendocrinology* (2011); 94: 37-38.
Pommier R F et al.	Impact of prior chemotherapy on progression-free survival in patients (pts) with advanced pancreatic neuroendocrine tumors (pNET): Results from the RADIANT-3 trial.	*Journal of Clinical Oncology* (2011); 29(15).
Shah M H et al.	Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Updated results of a randomized, double-blind, placebo-controlled, multicenter phase III trial (RADIANT-3).	*Journal of Clinical Oncology* (2011); 29(4).
Shah M H et al.	Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Impact of somatostatin analog use on progression-free survival in the RADIANT-3 trial.	*Journal of Clinical Oncology* (2011); 29(15).
Shah M H et al.	Treatment of pancreatic neuroendocrine tumors (pNET) with everolimus: Improved progression-free survival compared with placebo (RADIANT-3).	*Pancreas* (2011); 40(2): 331-332.
Strosberg J et al.	Prognostic value of chromogranin a and neuron-specific enolase in patients with advanced pancreatic neuroendocrine tumors (pNET): Phase III RADIANT-3 study results 2011 ACG presidential poster.	*American Journal of Gastroenterology* (2011); 106: S58.
Strosberg J et al.	Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Updated results of a randomized, double-blind, placebo-controlled, multicenter, phase III trial (RADIANT-3).	*Journal of Clinical Oncology* (2011); 29(15).
Wolin E et al.	Updated results from the randomized, double-blind, placebo-controlled, multicenter, phase III trial (RADIANT-3) of everolimus in patients with advanced pancreatic	*American Journal of Gastroenterology* (2011); 106: S59

Trial ID/ First author	Protocol title/ Publication title	Publication citation
	neuroendocrine tumors (pNET).	
Yao J C et al.	A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus in patients with advanced pancreatic neuroendocrine tumors (PNET) (radiant-3).	*Annals of Oncology* (2010); 21: viii4-viii5.
Yao J C et al	Everolimus for advanced pancreatic neuroendocrine tumors.	*New England Journal of Medicine* (2011); 364(6): 514-523.
Yao J C et al.	Effect of everolimus treatment on markers of angiogenesis in patients with advanced pancreatic neuroendocrine tumours (pNET) - Results from the phase III RADIANT-3 study.	*European Journal of Cancer* (2011); 47: S463.
A618-1111		
Deeks E D	Sunitinib: In advanced, well differentiated pancreatic neuroendocrine tumors.	*BioDrugs* (2011); 25(5): 307-316.
Hammel P et al	Evaluation of progression-free survival by blinded independent central review in patients with progressive, well-differentiated pancreatic neuroendocrine tumors treated with sunitinib or placebo.	*Pancreas* (2011); 40(2): 327.
Ishak J et al.	Overall survival (OS) analysis of sunitinib (SU) after adjustment for crossover (CO) in patients with pancreatic neuroendocrine tumors (NET).	*Neuroendocrinology* (2011); 94: 27-28.
Niccoli P	Updated Safety and Efficacy Results of the Phase III Trial of Sunitinib vs Placebo for Treatment of Pancreatic Neuroendocrine Tumors (NET).	*Journal of Clinical Oncology* (2010); 28(15)
Raoul J	Sunitinib (SU) vs placebo for treatment of progressive, well-differentiated pancreatic islet cell tumours: results of a phase III, randomised, doubleblind trial.	*Journal of Clinical Oncology* (2010); 28(15)
Raymond E	Cox Proportional Hazard Analysis of Sunitinib Efficacy Across Subgroups of Patients with Progressive Pancreatic Neuroendocrine Tumors.	*Journal of Clinical Oncology* (2010); 28(15)
Raymond E et al.	Updated results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of advanced pancreatic neuroendocrine tumors (NET).	*Journal of Clinical Oncology* (2010); 28(15)
Raymond E et al.	Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.	*New England Journal of Medicine* (2011a); 364(6): 501-513.
Raymond E et al.	Impact of baseline Ki-67 index and other baseline characteristics on outcome in a study of sunitinib (SU) for the treatment of advanced, progressive pancreatic neuroendocrine tumor (NET).	*Neuroendocrinology* (2011); 94: 41.
Raymond E et al.	Updated overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) of sunitinib (SU) versus placebo (PBO) for patients	*Journal of Clinical Oncology* (2011b); 29(15).

Trial ID/ First author	Protocol title/ Publication title	Publication citation
	(Pts) with advance unresectable pancreatic neuroendocrine tumors (NET).	
Valle J	Sunitinib versus Placebo for Treatment of Pancreatic Neuroendocrine Tumors; Impact of Somatostatin Analogue Treatment on Progression-free Survival.	*Annals of Oncology* (2010); 21(Suppl 8)
Valle J et al.	Updated overall survival data from a phase III study of sunitinib vs. placebo in patients with advanced, unresectable pancreatic neuroendocrine tumour (NET).	*European Journal of Cancer* (2011); 47:S462.
Van Cutsem E	Evaluation of Progression Free Survival by Blinded Independent Central Review in Patients with Progressive, Well-differentiated Pancreatic Neuroendocrine Tumors Treated with Sunitinib or Placebo.	*Annals of Oncology* (2010); 21(Suppl. 8)
Van Cutsem E et al.	Evaluation of progression-free survival by blinded independent central review in patients with progressive, well-differentiated pancreatic neuroendocrine tumors treated with sunitinib or placebo.	*Journal of Clinical Oncology* (2011); 29(4)
Vinik A	Patient-reported Outcomes in Patients with Pancreatic Neuroendocrine Tumors (NET) Receiving Sunitinib in a Phase III Trial.	*Journal of Clinical Oncology* (2010); 28(15)
Vinik A et al.	Sunitinib for treatment of pancreatic neuroendocrine tumors: Patient-reported outcomes and efficacy across patient subgroups in a phase III trial.	*Pancreas* (2011); 40(2): 334-335.
Vinik A et al	Progression-free survival (PFS) by blinded independent central review (BICR) and updated overall survival (OS) of sunitinib versus placebo for patients with progressive, unresectable, well differentiated pancreatic neuroendocrine tumor (NET).	*Pancreas* (2012); 41(2): 350.

8. Results of Trials

The results of the primary and secondary outcomes are presented below.

Results of progression free survival (PFS) outcomes in RADIANT-3 and A618-1111

	RADIANT-3		A618-1111	
	Everolimus 10 mg N=207	**Placebo N=203**	**Sunitinib 37.5 mg N=86**	**Placebo N=85**
PFS based on based on investigator assessment				
No. of PFS events, n (%)	**109 (52.7)**	**165 (81.3)**	**30 (35)**	**51 (60)**
Progression	95 (45.9)	158 (77.8)	27 (31)	48 (56)
Death	14 (6.8)	7 (3.4)	3 (3)	3 (4)
Censored	98 (47.3)	38 (18.7)	56 (65)	34 (40)
Hazard ratio (95% CI)	**0.35 (0.27, 0.45)[a]**		**0.42 (0.26, 0.66)**	
p value	p<0.001		p<0.001	
Event free at 6 months (%), (95% CI)	69.5 (62.4, 75.5)	31.9 (25.4, 38.5)	71.3 (60.0, 82.5)	43.2 (30.3, 56.1)
PFS (months), median (95% CI)	11.04 (8.41, 13.86)	4.60 (3.06, 5.39)	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)
Overall Survival at first data cut-off not adjusted for cross-over				
No. of events, n (%)				
Death	51 (24.6)	50 (24.6)	9 (10)	21 (25)
Censored	156 (75.4)	153 (75.4)	77 (90)	64 (75)
Hazard ratio (95% CI)	1.05 (0.71,1.55)[a]		0.41 (0.19, 0.89)	

NR = Not reported; RD = risk difference, NNT= number needed to treat, RR = relative risk.
Notes: [a] Second data cut-off and ITT analysis used for both studies.

There may have been some differences between the populations in the trials, although it was noted that these differences were based on very small numbers of events:

- The baseline risk (no. of PFS events in placebo) in RADIANT-3 was higher than in A618-1111 trial (78% vs. 50%) respectively. Although there was potential for confounding due to early termination of trial A618-1111, the placebo arms in both trials had similar treatment exposure (median 16.4 weeks everolimus, 16 weeks sunitinib)
- Concomitant somatostatin analogue use was higher in RADIANT-3 trial (49%/50%) than in A618-1111 (35%/38%) for treatment/placebo respectively.
- Prior chemotherapy was lower in RADIANT-3 trial (50%/50%) than in A618-1111 (66%/72%) for treatment/placebo respectively.
- Prior surgery was higher in the RADIANT-3 trial (100%/100%) than in A618-111 (88%/92%) for treatment/placebo respectively.

There was considerable uncertainty in the overall survival (OS) estimates due to the high degree of cross-over in both trials.

The results of the indirect comparison are presented in the table below. There were no statistically significant differences between the two treatments in terms of PFS and OS.

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.

A summary of results of the indirect comparison of safety outcomes is presented below.

There was no statistically significant difference with regard to "at least one AE" or "at least one Grade 3 or 4 AE" between everolimus and sunitinib treatment groups.

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%)

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that everolimus is non-inferior in terms of comparative effectiveness

and has a different but manageable comparative safety profile over sunitinib.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on non-inferiority claim for clinical effectiveness (PFS) and comparative safety, including additional costs/offsets for monitoring.

The equi-effective doses were estimated as everolimus 8.59 mg daily until progression or high toxicity and sunitinib 34.24 mg daily until progression or high toxicity. The doses were based on clinical trial evidence from RADIANT-3 and A618-1111.

In the base case, the monthly cost of everolimus was derived from the sum of the monthly cost of sunitinib and the additional monthly monitoring cost associated with sunitinib.

The submission assumed an equivalent cost for adverse events of everolimus and sunitinib in the economic evaluation.

The submission claimed that due to length of treatment differences in the trials the rate of adverse events in everolimus relative to sunitinib was likely to be overestimated. It was not possible to adjust for cross over in the safety profile. The PBAC noted that these estimates were based on very small numbers of events and the confidence intervals were correspondingly wide. The PBAC considered that it was therefore difficult to determine if there were real differences based on these data.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost-save per year to the Government of less than $10 million in Year 5.

For PBAC's view, see Recommendations and Reasons.

12. Recommendation and Reasons

The PBAC acknowledged there was a high clinical need for treatment for pancreatic neuroendocrine tumour (pNET), given the rarity of this type of tumour. The PBAC recalled from its March 2012 meeting it had previously deferred a submission for sunitinib on the basis of price for the pNET indication and subsequently rejected the submission at its July 2012 meeting on the basis of an unacceptably high and uncertain ICER compared to best supportive care (placebo).

The PBAC did not agree that sunitinib was the appropriate comparator. The PBAC recalled from its July 2012 meeting that sunitinib was not recommended as cost-effective for this indication. The PBAC considered that a comparison with best supportive care (including symptomatic treatment with somatostatin analogues) is currently the most relevant comparator to inform the cost effectiveness of everolimus on the PBS, in particular for patients with well or moderately-differentiated tumours.

The PBAC noted that the submission requested a broader restriction than sunitinib to include the treatment of moderately differentiated, in addition to well-differentiated pNET tumours.

In the RADIANT-3 trial (main supporting study), 16% of patients had moderately differentiated disease.

The PBAC noted that the basis of the submission was an indirect comparison of two randomised 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 (Trial A618-1111) via placebo. In RADIANT-3, 72.8% of patients initially randomised to placebo crossed over to treatment at progression, and after early termination of Trial A618-1111, 69.4% of placebo patients (both progressed and non-progressed) crossed over to active treatment. The results of RADIANT-3 demonstrated superiority of everolimus relative to placebo for progression free survival (PFS) outcomes [HR 0.35, (95% CI: 0.27, 0.45) p<0.001], a median 11.04 months for everolimus versus placebo 4.6 months [HR 0.35, (95% CI: 0.27, 0.45) p<0.001]. Results for Trial A618-1111 demonstrated superiority for sunitinib for PFS [HR 0.42 (95% CI: 0.26, 0.66) p<0.001], a median 11.4 months versus placebo 5.5 months.

In terms of overall survival (OS), median overall survival in RADIANT-3 was not reached. Based on the intention to treat (ITT) analysis in Trial A618-1111, superiority was demonstrated for sunitinib relative to placebo in with an [adjusted HR 0.499 (95% CI: 0.351, 0.947) p<0.001]. Median overall survival was 30.5 months and 24.4 months for sunitinib and placebo respectively.

The results of the indirect comparison for everolimus versus sunitinib show no statistically significant differences between the two treatments in terms of PFS and overall survival. The hazard ratio (HR) for the primary endpoint PFS was 0.83 (95% CI: 0.50, 1.40) The HR for overall survival was 1.21 (95% CI: 0.69, 2.12). The PBAC noted the submission did not attempt to adjust the overall results for crossover and that the early stopping and high cross-over make the interpretation of the indirect comparison difficult. Based on the evidence presented, the PBAC did not accept the submission's claim that everolimus is non-inferior to sunitinib in terms of clinical effectiveness. The PBAC considered the claim 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.

The PBAC noted that sunitinib and everolimus have different toxicities. In Trial A618-1111 the most common grade 3 or 4 adverse events in the sunitinib arm were neutropenia (12%), hypertension (10%), hand-foot syndrome (6%), and leukopenia (6%). Dose adjustments were required by 28% of patients but mean relative dose intensity was maintained at 91.3% suggesting that patients tolerated the treatment well. In RADIANT-3, the most common grade 3 or 4 drug-related adverse events were anaemia (8%), hyperglycaemia (8%), stomatitis (5%), thrombocytopenia, diarrhoea (5%), hypophosphatemia, and neutropenia (5%). Dose adjustments were required by 59% of patients with a relative dose intensity of 85.9%. Treatment duration was longer for everolimus (8.7 months) than sunitinib (4.6 months). For the indirect comparison of safety outcomes there was no statistically significant difference with regard to "at least one adverse event" or "at least one Grade 3 or 4 adverse event" between the everolimus and sunitinib treatment groups. Based on the evidence presented, the PBAC considered there was insufficient evidence to accept the submission's claim that everolimus is non-inferior to sunitinib in terms of comparative safety and may in fact be inferior. The PBAC also noted that the submission assumed no adverse event costs in the economic evaluation.

The PBAC noted the submission presented a cost minimisation analysis of everolimus versus sunitinib based on a non-inferiority claim for clinical effectiveness and comparative safety. However, as sunitinib had not been found to be cost-effective in the pNET population, the PBAC considered the cost minimisation analysis was not valid.

The PBAC noted the submission presented financial estimates based on the assumption of a shared market with sunitinib for pNET, however as sunitinib has not been recommended for PBS listing in this population, the PBAC considered the estimates invalid.

The PBAC expressed concern that in the event both sunitinib and everolimus be recommended for PBS listing for pNET, there is the possibility that clinicians may consider sequential use of these drugs. The PBAC noted that there are no clinical trials to support efficacy of sequential use and, in the event that sequential use became accepted practice, this may result in a two fold increase expenditure for patients with pNET.

The PBAC considered that a cost-effectiveness analysis versus placebo (best supportive care including symptomatic treatment with somatostatin analogues) would be a more appropriate approach. The PBAC considered that a substantial price reduction would be required to reduce the ICER to a more acceptable level.

The PBAC rejected the submission on the basis of an inappropriate comparator and resultant invalid cost minimisation analysis and an unacceptably high ICER.

The PBAC also 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 did not provide further comment.