PUBLIC SUMMARY DOCUMENT
Product: Sunitinib malate, capsules, 12.5 mg, 25 mg and 50 mg (base), Sutent®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought an Authority Required listing for the initial and continuing treatment of unresectable, well-differentiated pancreatic neuroendocrine tumour (pNET) in patients who are unsuitable for cytotoxic chemotherapy.

2. Background

Sunitinib had not previously been considered for this condition by the PBAC.

At its July 2008 meeting, the PBAC recommended an Authority Required listing of sunitinib for Stage IV clear cell variant renal cell carcinoma on the basis of acceptable cost-effectiveness compared with best supportive care. Listing was effective on 1 May 2009.

At its July 2009 meeting, the PBAC recommended sunitinib as an Authority Required listing for initial and continuing treatment of gastrointestinal stromal tumour after failure of imatinib mesylate treatment due to resistance or intolerance on the basis of high clinical need and a high but acceptable cost-effectiveness ratio compared with best supportive care. Listing was effective on 1 December 2009.

3. Registration Status

Sunitinib was TGA registered on 2 March 2011 for the treatment of unresectable, well-differentiated pNET.

Sunitinib is also indicated for the treatment of advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumour after failure of imatinib mesylate treatment due to resistance or intolerance.

4. Listing Requested and PBAC's View

Authority Required
Initial PBS-subsidised treatment of unresectable, well-differentiated pancreatic neuroendocrine tumour (pancreatic NET) in patients who are unsuitable for cytotoxic chemotherapy.

Authority Required
Continuing PBS-subsidised treatment of patients with unresectable, well-differentiated pancreatic neuroendocrine tumour (pancreatic NET) who have previously been issued with an authority prescription for sunitinib and who do not have progressive disease.

For PBAC's views, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Unresectable, well-differentiated pNET is a rare cancer in patients with a high degree of metastases and poor prognosis. The submission proposed that sunitinib would give these

patients a therapeutic option as currently there are no PBS-listed drugs available for the treatment of this condition.

The PBAC acknowledged there was a high clinical need for treatment for this rare type of tumour.

6. Comparator

The submission nominated best supportive care (placebo) as the main comparator. The PBAC agreed that the comparator was best supportive care.

Best supportive care in the A618-1111 trial could have comprised any of the following:

- Somatostatin analogues for symptomatic treatment.
- Hormone replacement therapy for adrenal or thyroid insufficiency.
- Bisphosphonates if bone metastases present prior to enrolment.
- Anti-inflammatory and narcotic analgesics as required.
- Anticoagulants up to 2 mg/day of warfarin for prevention of deep vein thrombosis.
- Palliative radiotherapy.

7. Clinical Trials

The evidence of effectiveness was based on a single trial, Study A618-1111. This study was designed to test the hypothesis that treatment with sunitinib plus best supportive care resulted in at least a 50% improvement in median progression free survival (PFS) over placebo plus best supportive care.

The published trials presented in the submission are shown in the table below.

Trial ID / First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
A618-1111 Raymond E	Sunitinib malate for the treatment of pancreatic neuroendocrine tumours.	*New England Journal of Medicine*. 2011. 364 (6): 501-513
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).	2010 American Society of Clinical Oncology Gastrointestinal Cancers Symposium. Abstract No. 127
Raoul J	Sunitinib (SU) vs placebo for treatment of progressive, well-differentiated pancreatic islet cell tumours: results of a phase III, randomised, double-blind trial.	*EJC Supplements*. 2009. 7 (2): 361
Niccoli P, et al.	Updated Safety and Efficacy Results of the Phase III Trial of Sunitinib vs Placebo for Treatment of Pancreatic Neuroendocrine Tumors (NET).	Oral presentation at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, USA, June 4–6, 2010. (Abstract 4000)

Raymond E, et al.	Cox Proportional Hazard Analysis of Sunitinib Efficacy Across Subgroups of Patients with Progressive Pancreatic Neuroendocrine Tumors.	Poster presentation at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago,IL, USA, June 4–6, 2010. (Abstract 4031)
Vinik A, et al.	Patient-reported Outcomes in Patients with Pancreatic Neuroendocrine Tumors (NET) Receiving Sunitinib in a Phase III Trial.	Oral presentation at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, USA, June 4–6, 2010. (Abstract 4003)
Valle J, et al.	Sunitinib versus Placebo for Treatment of Pancreatic Neuroendocrine Tumors; Impact of Somatostatin Analogue Treatment on Progression-free Survival.	Poster presentation at European Society for Medical Oncology (ESMO) Oct 2010 (846P)
VanCutsem 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.	Poster presentation at EMSO Oct 2010 (747P)
RTKC-0511-015 Kulke M et al.	Activity of sunitinib in patients with advanced neuroendocrine tumours.	*J of Clinical Oncology. 2008. 26: 3403-3410*

The submission stated that the efficacy results from trial RTKC-0511-015 were excluded due to the trial being a non-comparative study to evaluate the efficacy and safety of sunitinib. However, the quality of life data from the RTKC-0511-015 trial were used in the economic evaluation and a summary of safety data on sunitinib was included in the submission for completeness.

8. Results of Trials

The effectiveness was presented in three analyses:

- Clinical Study Report (CSR) dataset (progression free survival) – Intention to treat (ITT) included patients in the double-blind period prior to cross-over.
- CSR dataset (overall survival) – ITT included patients in the double-blind period, however in the analyses, some patients progressed and crossed-over to receive open-label sunitinib prior to early termination of the trial.
- Extension dataset (overall survival) – ITT included all placebo patients who crossed-over.

The key effectiveness results for progression free survival (PFS) and overall survival (OS) are presented below for the CSR dataset.

Summary of main results (PFS and OS) from the direct randomised trial and the extension study.

Variable	Number of events		Hazard ratio (HR)	p-value
	Sunitinib N = 86	Placebo N = 85		
Progression-free survival – CSR dataset (ITT population)				
Progression or death due to any cause while on study Objective progression Death without progression	30 (34.9%) 27 (31.4%) 3 (3.5%)	51 (60.0%) 48 (56.5%) 3 (3.5%)	0.418 (0.263, 0.662)	<0.001
Median progression-free survival (months)	11.4	5.5		
Overall survival - CSR dataset (ITT population)				
Died	9 (10.5%)	21 (24.7%)	0.409 (0.187, 0.894)	0.0204
Alive	77 (89.5%)	64 (75.6%)		
1st quartile for time to death (months)	20.6	9.7		
Median time to death (months)	20.6	NR		

The results for the CSR dataset indicated that there was a clinically significant improvement (P < 0.001) in PFS in favour of sunitinib compared with placebo. The median PFS was 11.4 months in the sunitinib arm and 5.5 months in the placebo arm, with a hazard ratio of 0.418 (95%CI: 0.263, 0.662). The PBAC considered that the estimates of the gain in PFS of 5.9 months (and HR for PFS=0.418) could be overestimated due to the early termination of the A618-1111 trial.

There were statistically significant differences in the overall survival between treatments in the CSR dataset (HR=0.409; 95%CI: 0.187, 0.894; P = 0.0204) (which is used in the base case of the economic model) but not in the extension dataset.

For PBAC's views, see Recommendations and Reasons.

A greater proportion of sunitinib treated subjects (11 [13.3%]) experienced treatment related serious adverse events than placebo (6 [7.3%]). These included neutropenia (experienced by 12.0% of sunitinib patients but no placebo patients), hypertension (9.6% of sunitinib but no placebo patients), leukopenia (6.0% of sunitinib patients but no placebo patients), and palmar-plantar erythrodysaesthesia syndrome (6.0% of sunitinib patients but no placebo patients).

9. Clinical Claim

The submission claimed that sunitinib is superior in terms of clinical effectiveness over best supportive care/placebo in the treatment of unresectable pancreatic neuroendocrine tumours. The submission also described sunitinib as inferior in terms of treatment related serious adverse events over best supportive care/placebo. Based on the supporting data, this description was reasonable.

10. Economic Analysis

A stepped economic evaluation was presented and was based on a ten-year single cohort Markov model with three health states – non-progression; progression; and death. The

cycle length of the model was 3 months. The outcomes used in the model were life years gained (LYG) and quality adjusted life years gained (QALYs).

Median time to tumour progression was used to generate progression-free years, based on the analysis of the CSR dataset (double blinded period of A618-1111 trial).

The modelled economic evaluation incorporated the modelled and extrapolated sunitinib survival data (from the an extension study of the A618-1111 trial) and the placebo survival data generated by applying the reciprocal of the mortality hazard ratio from the CSR dataset (double blinded period of A618-1111) trial to the sunitinib curve. Modelled tumour progression data were used to generate the proportions of patients with and without tumour progression, so that unit costs and utilities could be applied to the progression and non-progression health states of the model.

The economic evaluation included serious adverse events in the model with an additional cost to account for this additional safety concern.

Based on the structure and assumptions used in the submission's model, sunitinib treatment of pNET was associated with an incremental cost per life year gained in the range of $45,000 - $75,000 and an incremental cost per QALY gained in the range of $45,000 - $75,000 compared with placebo over a ten-year time period. The key drivers of the model were OS (HR=0.409) and quality of life estimates.

Sensitivity analyses indicated that the model was most sensitive to assumptions regarding the survival hazard ratio used to derive the placebo mortality rate in the model and utilities. The submission estimated the ICER to be in the range of $45,000 - $75,000/QALY (HR =1 at month 30; 10 year horizon, PFS =1 at month 12 month) and using a utility value of 0.5 to be in the range of $75,000 - $105,000/QALY, which was considered to be highly uncertain.

For PBAC's views, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The total net cost to the PBS was estimated in the submission to be less than $10 million in year 5.

12. Recommendation and Reasons

The PBAC acknowledged there was a high clinical need for treatment for this rare type of tumour. The PBAC agreed that the comparator was best supportive care.

The PBAC considered that the initial requested restriction should specify monotherapy as there are no data on combination use with cytotoxic therapies, and that the wording should include the following: "*metastatic* or unresectable well differentiated *malignant* pancreatic neuroendocrine tumour (pancreatic NET) *who are symptomatic (despite somatostatin analogues) or have documented disease progression*". The PBAC noted that 50% of patients in the key study had a functional tumour and 35-38% of patients in the study received somatostatin analogues prior to or concomitantly with sunitinib. Therefore, there should be a requirement that patients with functional tumours have

symptoms treated with somatostatin analogues prior to treatment with sunitinib. The PBAC noted that WHO system classified tumours on the basis of histological grade and that Grade 1 tumours are benign but may occasionally display low malignant potential and that WHO Grade 3 tumours are not considered to be the same disease. While restricting sunitinib to WHO 2 would capture most eligible patients, the PBAC noted that this may disadvantage a small group who were classified as WHO 1 and in whom treatment was considered appropriate. Inclusion of the word "malignant" may best identify those patients who would potentially benefit most from sunitinib. The PBAC believed that the drug should not be seen as a substitute for effective surgical intervention. Therefore, patient selection was important and patients with metastatic or unresectable disease who are symptomatic or have progressive disease are probably more likely to benefit from treatment with sunitinib. Continuing therapy should only be in patients without disease progression which is consistent with the clinical trial.

The key clinical study in the submission was A618-1111 and the results for the Clinical Study Report (CSR) dataset indicated that there was a clinically significant improvement ($P < 0.001$) in PFS (progression free survival) in favour of sunitinib compared with placebo. The median PFS was 11.4 months in the sunitinib arm and 5.5 months in the placebo arm, with a hazard ratio of 0.418 (95%CI: 0.263, 0.662). The PBAC considered that the estimates of the gain in PFS of 5.9 months (and HR for PFS=0.418) could be overestimated due to the early termination of the A618-1111 trial.

There were statistically significant differences in the overall survival between treatments in the CSR dataset (HR=0.409; 95%CI: 0.187, 0.894; $P = 0.0204$) (which is used in the base case of the economic model) but not in the extension dataset. The PBAC noted that both analyses of overall survival were confounded by patient cross-over from placebo to sunitinib treatment (30% of placebo patients had crossed-over to open-label sunitinib by Week 13, increasing to 65% by Week 52). However, the PBAC considered that due to early cross over there is a high level of censoring in the placebo arm of the trial and as a result there was a high degree of uncertainty in the magnitude of the benefit in terms of overall survival.

The PBAC agreed that the extrapolation of the hazard ratio (HR=0.409) from the relatively short timeframe of the A618-1111 trial, to the 10-year timeframe of the economic model, was a major source of uncertainty. The PBAC noted that the submission used an incremental life years gained of 1.212 in the economic evaluation and considered this an overestimate.

The utility for the progression-free and post-progression health states (0.852 for both placebo and sunitinib) were based on the of EQ-5D data from a supportive trial (RTKC-0511-015). The PBAC noted that thirty eight (57%) patients withdrew from trial RTKC-0511-015 due to 'lack of efficacy' or 'consent withdrawn', with most of these exiting by the end of cycle 6 which suggested that the patients remaining in the trial were healthier than those that exited. The PBAC considered that the utilities from this sample were likely to be overestimated and noted that a MVH National Survey (1993), a nationally representative sample in the United Kingdom, estimated utility weights for 55-64 yr olds (including all morbidity) of 0.80, which was lower than that estimated in trial RTKC-

0511-015. The PBAC also noted that a disutility of 0.1 was applied in the first cycle that a serious adverse event occurred.

The PBAC noted that the key drivers of the economic model were overall survival (OS) (hazard ratio=0.409), which was considered implausible, and quality of life estimates with an incremental cost per QALY gained (base case) in the range of $45,000 -$75,000 compared with placebo over a ten-year time period. The sensitivity analyses indicated that the model was most sensitive to assumptions regarding the survival hazard ratio used to derive the placebo mortality rate in the model and utilities. The submission estimated the ICER to be in the range of $45,000 - $75,000/QALY (HR =1 at month 30; 10 year horizon, PFS =1 at month 12 month) and using a utility value of 0.5 to be in the range of $75,000 - $105,000/QALY, which was considered to be highly uncertain.

The PBAC therefore rejected the submission on the basis of a high and uncertain incremental 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 sponsor has no comment.