PUBLIC SUMMARY DOCUMENT
Product: Sunitinib malate, capsule, 12.5 mg, 25 mg and 50 mg (base), Sutent®
Sponsor: Pfizer Australia Pty Limited
Date of PBAC Consideration: March 2012

1. Purpose of Application

The re-submission requested an extension to the current Authority Required listing to include the initial and continuing treatment of metastatic, unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (or carcinoma) (pancreatic NET) in a patient who is symptomatic (despite somatostatin analogues) or has documented disease progression.

2. Background

In July 2011, the PBAC rejected a submission requesting an Authority Required listing of sunitinib for pancreatic NET on the basis of a high and uncertain incremental cost-effectiveness ratio. The PBAC however acknowledged there was a high clinical need for treatment for this rare type of tumour.

A copy of the Public Summary Document (PSD) from the July 2011 meeting is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-sunitinib-malate-july11

3. Registration Status

Sunitinib was TGA registered on 2 March 2011 for the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET).

4. Listing Requested and PBAC's View

Authority Required

Initial PBS-subsidised treatment as monotherapy, of metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (or carcinoma) (pancreatic NET) in a patient who is symptomatic (despite somatostatin analogues) or has documented disease progression.

Continuing PBS-subsidised treatment as monotherapy, of metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (or carcinoma) (pancreatic NET) in a patient who has previously been issued with an authority prescription for sunitinib and who does not have progressive disease.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Unresectable, well-differentiated pancreatic NET is a rare cancer with a high degree of metastases and a poor prognosis. The submission noted that surgical resection is not a feasible treatment option in most cases of pancreatic NET as pancreatic NET is a highly proliferative tumour and is often diagnosed at an advanced stage.

The submission proposed that sunitinib would provide a therapeutic option for pancreatic NET as currently there are no PBS-listed drugs available for the treatment of this condition.

6. Comparator

The submission nominated best supportive care (placebo) as the main comparator. This was previously accepted by the PBAC.

7. Clinical Trials

The re-submission included updated overall survival data from one of the randomised trials originally presented with the July 2011 submission. This included an additional 6 months follow-up data (from 30 months to 36 months) where median overall survival (OS) was reached.

Trial ID / First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
A618-1111 Valle J, et al.	Updated Overall Survival from a Phase III Study of Sunitinib vs Placebo in patients with Advanced, Unresectable Pancreatic Neuroendocrine Tumour	Poster presentation at European Society for Medical Oncology (ESMO) Oct 2011 (Abstract 6569)

No changes were made to the trial data presented in the previous submission regarding progression free survival (PFS). Publication details of these trials have been previously reported in the July 2011 PSD.

8. Results of Trials

The key effectiveness results from Study A618-1111 for PFS and OS are presented below for both the Clinical Study Report (CSR) dataset, ESMO dataset and the extension dataset.

Summary of main results (PFS and OS) from the direct randomised trial (including the updated) 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		
Overall survival- ESMO Dataset (ITT population) no adjustment for crossover				
Died	34 (39.5)	39 (45.9)		
Alive	52 (60.5)	46 (54.1)		

Variable	Number of events		Hazard ratio (HR)	p-value
	Sunitinib N = 86	Placebo N = 85		
1st quartile for time to death (months)	30.5	24.4	0.737 (0.465, 1.168)	0.1926
Median time to death (months)	NR	NR		

The results for the CSR dataset indicated that there was a clinically significant improvement in PFS in favour of sunitinib compared to placebo. The median PFS was 11.4 months in the sunitinib arm and 5.5 months in the placebo arm (HR=0.418 [95% CI: 0.263, 0.662]).

The most common treatment-related (all-causality) grade 3/4 adverse events in the sunitinib arm were neutropenia (12%), hypertension (10%), hand-foot syndrome (6%), and leukopenia (6%). In the placebo arm, the most common AEs were abdominal pain (10%), fatigue (9%), and back pain (5%).

For PBAC's view of these results, see Recommendation and Reasons.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed that sunitinib is superior in terms of comparative effectiveness and inferior in terms of comparative safety, compared to optimal background therapy (OBT).

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The stepped economic evaluation 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 are life years gained (LYG) and quality adjusted life years gained (QALYs). This was unchanged from the previous submission.

The modelled economic evaluation incorporated the modelled and extrapolated sunitinib survival data (from the ESMO study of the A618-1111 trial) and the placebo survival data generated by applying the reciprocal of the mortality hazard ratio from the ESMO Dataset of the A618-1111 trial to the sunitinib curve. This was updated as a result of the additional 6 months of follow-up data and median OS being reached.

In the base case, a constant hazard ratio (HR) is applied after the trial period. The Pre-Sub-Committee Response (PSCR) from the sponsor argued that the HR from the ESMO dataset is representative of an average measure of survival as it captures the survival outcomes of patients who were no longer on treatment. The PSCR considered that tapering this HR was not required as it already accounts for the impact of patients discontinuing treatment.

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. This was unchanged from the previous submission: The re-submission still assumed that 25.9% of patients who progress continue on a dose of 32.9 mg/day for 138 days.

Based on the structure and assumptions used in the submission's model, sunitinib treatment of pancreatic NET was associated with an incremental cost per life year gained of between $45,000 and $75,000 (increased from the previous submission) and an incremental cost per QALY gained of between $45,000 and $75,000 (increased from the previous submission), compared with placebo over a ten-year time period. The key driver of the model was utility estimates.

The results of the sensitivity analyses indicated that the model was most sensitive to utility values. The PBAC considered that the utility estimates are over-estimated and agreed that the model should allow a utility decrement for disease progression.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 per year in Year 5, at an estimated net cost per year to the PBS of less than 10 million per year in Year 5.

12. Recommendation and Reasons

The PBAC noted the sponsor's request in its Pre-PBAC Response for PBAC to consider the applicability of the Rule of Rescue for this submission. However, as sunitinib is for the treatment of metastatic disease and not treatment in the adjuvant setting the PBAC considered that there is no expectation of "rescue" of patients as they will ultimately succumb to their disease. The PBAC also noted that there are other treatment options currently available for this disease including surgery, used to control the disease initially in some patients. Chemotherapy agents may also be used to treat the disease, however, the effect may not be durable. Agents are also available to treat the symptoms of the disease, including octreotide. Therefore, the PBAC did not consider that the Rule of Rescue applied to this submission.

The PBAC noted that four issues of concern in the July 2011 submission were the restriction, the estimation of overall survival, the extrapolation of the hazard ratio and the utility estimates. The PBAC considered that the sponsor had addressed the issues relating to the restriction in the resubmission. However, there was still uncertainty regarding surrounding the survival gain. The PBAC noted that the submission presented updated survival data from Study A618-1111, provided in four analyses. Using the Clinical Study Report (CSR) dataset, the PBAC noted that there was a clinically significant improvement ($P < 0.001$) in PFS (progression free survival) in favour of sunitinib compared with placebo (11.4 months in the sunitinib arm and 5.5 months in the placebo arm), hazard ratio of 0.418 (95%CI: 0.263, 0.662). However, there is a high likelihood that this hazard ratio is over-estimated due to the multiple interim analyses and early stopping of the trial based on the most recent of these analyses. There were also 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).

The PBAC noted that the parametric model to estimate overall survival used sunitinib overall survival data from the ESMO dataset, which was extrapolated out to 10 years and adjusted for crossover using three statistical analyses with hazard ratios ranging from 0.416 to 0.499. The PBAC noted that the rank-preserving structural failure time (RPSFT) estimates (HR 0.499) used in the economic model were the most conservative, which resulted in an adjusted median OS for placebo of 17.5 months, with an incremental survival benefit of 13 months in favour of sunitinib. The PBAC agreed with the ESC that overall the results suggest that sunitinib is likely to have some survival benefit, but the size of the effect is unknown due to patient cross-over within the trial. The PBAC considered that the effect is probably less than the adjusted hazard ratios suggest and may be closer to the unadjusted benefit which is similar to the progression-free survival benefit (6.1 months vs. 5.9 months, respectively).

The PBAC considered that the time horizon of 10 years used in the economic evaluation was an overestimate for a patient group with progressive metastatic disease and a relatively high progression rate. The PBAC further considered that it is not reasonable for the HR in the base case, applied after the trial period, to be constant over time as relating the hazard to progression rather than the cessation of treatment would likely increase the HR over time. In addition, the HR derived from the ESMO dataset only accounts for a 36 month period which is unlikely to be representative of the treatment effect over the modelled time horizon.

The PBAC considered that the utility estimates are over-estimated and agreed that the model should allow a utility decrement for disease progression. The PBAC noted that the sunitinib submission to the Scottish NHS applied utility values of 0.73 pre-progression and 0.596 post-progression. The PBAC noted that multivariate analyses conducted during the evaluation using differential utility weights for pre- and post-progression (0.73 and 0.596, respectively), and assuming a tapered treatment effect, demonstrated that the ICER could be substantially greater than the base case (in the range of between $75,000 and 105,000/QALY compared to the base case ICER of between $45,000 and 75,000/QALY).

The PBAC acknowledged that the pNET patient population is small and the clinical need is high, with similarities to the GIST population. The PBAC recalled it had recommended listing sunitinib for GIST in July 2009 with an ICER of between $45,000 and 75,000/QALY, with similarly favourable estimates of incremental gains in overall survival, but without the favourable incremental gains in progression-free survival and the favourable utility assumptions. The PBAC considered that if an ICER similar to the GIST indication is achieved after a substantial price reduction, the PBAC may then be able to consider the PBS listing of sunitinib for pNET.

The PBAC therefore deferred consideration of the submission pending negotiation with the sponsor regarding price of sunitinib for this indication.

Recommendation:
Defer

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 is working with the PBAC to achieve PBS listing of sunitinib for patients with pNET