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: March 2008

1. Purpose of Application

To seek an Authority Required listing for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate due to resistance or intolerance.

2. Background

At the March 2007 meeting, the PBAC deferred consideration of the submission for sunitinib pending the provision of further information to demonstrate that sunitinib is a cost effective treatment for gastro-intestinal tumour (GIST) after failure of imatinib. *(See Public Summary Document for March 2007).*

3. Registration status

Sunitinib malate is registered by the TGA for the treatment of:

- Advanced renal cell carcinoma; and
- Gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

4. Listing requested and PBAC's view:

Authority required

For the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Note: It is recommended that treatment with sunitinib be discontinued if tumour progression occurs.

The PBAC did not comment on the requested restriction.

5. Clinical place for the proposed therapy

Gastrointestinal stromal tumour (GIST) is an uncommon visceral sarcoma that arises predominantly in the gastrointestinal tract. Sunitinib will provide an alternative treatment for those patients with GIST who cannot tolerate imatinib, or who have tumours that are resistant to, or become resistant to, this drug.

6. Comparator

The submission nominated best supportive care (placebo) as the main comparator. This was as indicated by the PBAC at the March 2007 meeting.

7. Clinical trials

The re-submission presented no new trials. The single key trial was Trial 1004; a randomised, multicentre, international, phase III study of sunitinib vs placebo as first-line therapy in subjects with malignant gastrointestinal stromal tumour (GIST), who had failed treatment on imatinib or were intolerant of imatinib. Subjects received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily sunitinib administration followed by 2 weeks off treatment (4/2), or matching placebo.

The trial was published at the time of the submission as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Study 1004/ Demetri G (2006)	Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial.	The Lancet. 2006. 368 1329-38
Casali (2006)	Updated results from a phase III trial of sunitinib in GIST patients (pts) for whom imatinib (IM) therapy has failed due to resistance or intolerance.	J of Clin Oncol. 2006. ASCO Annual Meeting Proceedings Part 1. 24 (18S) (Abstract 9513)

8. Results of trials

The key results from study 1004, time to tumour progression (TTP), progression free survival (PFS) and overall survival (OS) are presented in the table below.

Time to tumour progression (TTP), Progression-free survival (PFS) and Overall Survival (OS) (ITT population) – study 1004 (interim analysis).

Variable	Number of events		Hazard ratio	p-value
	Sunitinib n (%)	Placebo n (%)		
	N = 207	N = 105		
Time to tumour progression (TTP)				
TTP events; crude rate n (%)	82 (39.6%)	67 (63.8%)		
TTP-free patients; crude rate n (%)	96 (46.4%)	26 (24.8%)		
Patients with data not available	29 [a] (14.0%)	12 [a] (11.4%)		
TTP median time to progression; weeks (95% CI)	27.3 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.329 (0.233 to 0.466)	<0.001
Progression-free survival (PFS) failure events i.e. tumour progression or death				
PFS failure events; crude rate n (%)	89 (43.0%)	70 (66.7%)		
PFS patients; crude rate n (%)	89 (43.0%)	23 (21.9%)		
Patients with data not available	29 [a] (14.0%)	12 [a] (11.4%)		
PFS median time to PFS-failure, weeks (95% CI)	24.1 (11.1 to 28.3) [b]	6.0 (4.4 to 9.9) [b]	0.333 (0.238 to 0.467)	<0.001
Overall survival (OS)				
Total deaths (any cause); crude rate n (%)	29 (14.0%)	27 (25.7%)		
Alive patients; crude rate n (%)	178 (86.0%)	78 (74.3%)		
Median time to death (any cause), weeks (95% CI)	median not reached	median not reached	0.491 (0.290 to 0.831)	0.007

a Core radiology laboratory data on tumour status were n/avail at time of interim analysis (29 and 12 patients receiving sunitinib and placebo, respectively).

b There is a small discrepancy in the results reported for PFS in the study report for Study A618-1004 and the published Lancet paper (Demetri, 2006). The Sponsor confirmed that the correct values are those reported in the published Lancet paper.

The results between TTP and PFS are very similar, as PFS was dominated by progression events rather than deaths. Both TTP and PFS were significantly greater in patients treated with sunitinib than in those in the placebo group.

The Kaplan-Meier curve for overall survival, based on the trial data (i.e. without extrapolating the time horizon), suggested that the benefit likely to be achieved with sunitinib might be roughly of the order of 10 weeks up to a maximum of 14 weeks.

No new toxicity data were presented in the re-submission. The rates of treatment-related serious adverse events (SAEs) from study 1004 were 19.8% for sunitinib vs 4.9% for placebo.

For PBAC's comments on these results see Recommendation and Reasons.

9. Clinical claim

The submission described sunitinib as superior in terms of comparative effectiveness over best supportive care (BSC), but more toxic given the rates of treatment-related serious adverse effects (SAEs) of sunitinib 19.8% and placebo 4.9%.

The PBAC accepted that based on the supporting data for progression free survival, this description was reasonable, and might be reasonable for overall survival. However, the size of the gain in overall survival was uncertain given the decision to unblind the study before median survival was reached.

10. Economic analysis

A new modelled economic evaluation was presented in the resubmission. The previous submission presented a cost-minimisation analysis.

The trial based economic evaluation estimated an incremental cost-effectiveness ratio of between $15,000 and $45,000 per progression free survival-year for sunitinib compared to BSC/placebo.

The Pre-Sub-Committee response addressed several numerical errors and issues of concern to provide a new base case for the model. The changes increased the base case incremental cost-effectiveness ratios (ICERs). The ICER per for life year gained (LYG) was between $75,000 and $105,000 and the ICER per quality adjusted life year (QALY) gained was between $105,000 and $ 200,000.

The results of the sensitivity analyses indicated that the model was most sensitive to the proportion of patients continuing sunitinib following tumour progression, continuous dosing and utilities.

In line with the argument previously presented to the PBAC that a large proportion of GIST patients treated with imatinib do not discontinue therapy despite experiencing disease progression while on imatinib therapy, the Pre-Sub-Committee response included costs for continued use of imatinib in the placebo arm to offset this increase, which resulted in ICERs of in the range of $45,000 to $75,000 per LYG and $75,000 to $105,000 per QALY.

For PBAC's views on the economic analysis see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients per year to be less than 10,000, at a net cost of to government of less than $10 million per year.

12. Recommendation and Reasons

The PBAC recognised the clinical need for additional treatments for this condition beyond failure with imatinib.

The clinical evidence submitted in support of sunitinib came from a well conducted, randomised, double-blind comparison of sunitinib and placebo in patients with metastatic or unresectable GIST having failed on imatinib (study 1004). The primary outcome of this trial was time-to-progression (TTP). At the first interim analysis, the median TTP was 27.3 weeks for sunitinib compared with 6.4 weeks for placebo (hazard ratio: 0.329, 95% CI: 0.233, 0.466, p<0.001). The results of the secondary outcome, progression-free survival, were very similar to the TTP results, a not-unexpected finding as the large majority of events were progressions rather than deaths. Overall survival was also significantly better in the sunitinib than in the placebo group at the first interim analysis (hazard ratio: 0.491, 95% CI: 0.290-0.831, p=0.007). The Committee acknowledged that the decision to un-blind the study following the first interim analysis and to offer sunitinib to all patients on placebo biased later overall survival analyses towards the null. Estimated survival from the Markov model in the submission of approximately 3.3 months was a reasonable estimate given the evidence.

The PBAC noted the comparator was no longer imatinib and accepted BSC/placebo as the main comparator, as previously suggested by the Committee. In March 2007, the PBAC considered that although imatinib may be an appropriate comparator according to the 2006 PBAC Guidelines as the therapy likely to be replaced in practice, the cost-effectiveness of continuing imatinib at elevated doses in patients with metastatic or unresectable GIST who have failed imatinib was unknown. Sensitivity analyses introduced during the evaluation of the current re-submission, which include a 40% cost-offset for continued imatinib treatment, use the inadequately supported assumption that treatment with imatinib in eligible patients is no better than placebo.

To determine the impact of treatment with sunitinib on overall survival, the economic model adopted a health state structure and follows patients out to a maximum of 5 years in 20 quarterly cycles; a point at which virtually all patients have progressed and the majority have subsequently died.

The rates of progression were based on the observed TTP rate from the trial. The same hazard ratio of 0.329 was continued for the life of the model. In this group of patients the PBAC considered it is likely that treatment resistance will build up over time, so that continuing to accrue the benefit that was seen in the trial data was inappropriate. This assumption was adjusted in sensitivity analyses to a HR = 1 after the trial period and further explored during the evaluation with the treatment benefit being maintained for one year and two years as per the advice from PBAC in March 2007. However, the sensitivity analysis shows that changing the HR to 1 has little effect on the modelled estimate of efficacy. This is because all the progression events happen early in the model.

The PBAC considered the submission's Markov model to be more informative than the direct extrapolation of overall survival data requested during evaluation. This was for two main reasons:

- early cross-over in the trial; and
- events in the trial were not deaths. Only 18% of patients had died at the time of the interim analysis. In comparison 48% had tumour progression.

The uncertainty of extrapolating overall survival with so few observations in this context outweighed the uncertainty associated with extrapolating survival from pooled mortality rates for progressors and non-progressors by applying the tumour progression rates. One or two changes in the number of deaths had a substantial impact on any ICER calculated from direct extrapolation. In line with this, the PBAC also agreed that ignoring the final quarter of mortality data for non-progressors (less than 10% of patients) in the Markov model was appropriate.

The main drivers in the model which were of concern to the PBAC were:

- continuing sunitinib use beyond tumour progression. The base case assumes 9.2% of patients will continue sunitinib post-progression, the same rate as observed in the trial. It is likely that this rate will be higher in clinical practice. The PBAC noted that the expert opinion provided in the Pre-Sub-Committee response suggested one third of patients would continue sunitinib post-progression for a period of time.
- having different utilities for progression for both sunitinib and placebo. The PBAC did not see any reason for the utilities to be more favourable with sunitinib.
- continuing imatinib treatment as a cost-offset in the placebo arm. The PBAC acknowledged that there would be some continued use of imatinib in this patient group, but considered that the treatment benefit would be higher than placebo. Therefore, the ICERs produced from sensitivity analyses which include a percentage of imatinib use would be underestimated. The assumed 40% continued use based on 2/5 surveyed clinicians is also uncertain.

The PBAC rejected the submission based on an unacceptably high and uncertain ICER. The uncertainty was mainly due to the impact of continued sunitinib post-progression. The base case ICERs of $75,000 to $105,000 per extra LYG and $105,000 to $200,000 per extra QALY gained would be higher with a greater proportion of continued sunitinib use post-progression. While some offset for continued use of imatinib may be appropriate and make the ICER more favourable, the PBAC believed the treatment effect should be attenuated against the effect of sunitinib. Continued use of either treatment should be in similar proportions (i.e. not 40% for imatinib and only 9.2% for sunitinib).

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 notes the PBAC's view that the cost effectiveness ratio is too high and will consider its position regarding any future course of action.