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 2007

1. Purpose of Application

The submission sought a Section 100 Authority Required listing for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate due to resistance or intolerance.

2. Background

This drug has not previously been considered by the PBAC.

3. Registration Status

Sunitinib mesylate was registered by the TGA on 14 September 2006 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

Section 100 Authority required (Special Authority Program)
Treatment of adult patients with a metastatic or unresectable malignant gastrointestinal stromal tumour (GIST) after failure of PBS-subsidised imatinib mesylate treatment due to resistance or intolerance.

The PBAC did not comment on the restriction.

5. Clinical Place for the Proposed Therapy

GIST is rare 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 continued use of imatinib mesylate 600 mg as the main comparator.

See Recommendation and Reasons for the PBAC's view.

7. Clinical Trials

The submission presented across-study comparisons of patients in the sunitinib arm of Trial 1004 and three cohorts of patients ("crossover cohorts") from three imatinib trials (Verweij/Zalcberg, Rankin, and Demetri given higher dose imatinib (600 mg or 800 mg) because they had shown tumour progression on imatinib 400 mg. Trial 1004 was a double-blind, Phase III comparison of sunitinib versus placebo in patients with metastatic or unresectable GIST having failed on imatinib. The imatinib trials compared 400 mg and 800 mg or 400 mg and 600 mg. No common comparator was available for use. This method was called an "indirect comparison" in the submission. The PBAC noted the ESC advice that it was a non-randomised comparison, so could not control for unsuspected or unknown confounders, and it was an across-study comparison with no common comparator to serve as an internal control. Both lessened the validity. There was also possible selection bias in the crossover cohorts because there were substantial numbers of patients eligible for crossover who did not enter the cohorts.

The PBAC was advised patients enrolled in the trials may not have been representative of the patients eligible under the requested PBS listing, which did not specify resistance to 400 mg/600 mg imatinib. The failure doses of imatinib in the sunitinib trial were: 400 mg or less: 19%, 600 mg: 16%, 800 mg 56%, >800 mg 9%. While all the patients in the cross-over cohorts failed at 400 mg.

The trials published at the time of the submission were 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)
Zalcberg (2005)	Outcome of patients with advanced gastrointestinal stromal tumours crossing over to a daily imatinib dose of 800mg after progression on 400mg.	Eur J of Cancer. 2005. 41 1751-1757
Verweij (2004)	Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial.	The Lancet. 2004. 364 1127-134
Rankin (2004)	Dose effect of imatinib (IM) in patients (pts) with metastatic GIST - Phase III Sarcoma Group Study S0033.	J of Clin Oncol. 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 22 (14S) (Abstract 9005)
Demetri (2002):	Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors.	NEJM. 2002. 347 (7) 472-80

8. Results of Trials

The results of the key analysis comparing median progression-free survival (PFS) in the sunitinib arm of Trial 1004 and the three crossover cohorts are summarised in the tables below. PFS analyses were time-to-first event comparisons where either progression or death qualified as an event, and the median PFS values determined from the Kaplan-Meier curves. Because the Demetri crossover cohort was small (n=9) a separate analysis of its median PFS compared to the sunitinib arm was not presented.

Median PFS of sunitinib arm (Trial 1004) and three imatinib crossover cohorts

Patient group (number, number eligible)	**Median PFS**
Sunitinib arm of Trial 1004(n=207)	24.1 wks
Verweij/Zalcberg crossover cohort (n=133 of 247 eligible)	11.6 wks
Rankin crossover cohort (n=88 of 164 eligible)	17.4 wks
Demetri crossover cohort (n=9 of 12 eligible)	14.5 wks
Patient groups being compared	**Difference in median PFS**
Sunitinib – Verweij/Zalcberg	18.1 wks
Sunitinib – Rankin	6.7 wks
Sunitinib – all three crossover cohorts	9.6 wks

The relative and absolute risk reductions of the same PFS events in the sunitinib arm of Trial 1004 compared to the three crossover cohorts are shown below.

Results of relative and absolute risk reduction of progression/death: Sunitinib arm of Trial 1004 and imatinib crossover cohorts

Comparison	**Relative risk reduction [95% CI]**	**Absolute risk reduction [95% CI]**
Sunitinib vs imatinib (Verweij/Zalcberg)	27.6% [10.6%, 41.3%]	16.4% [5.7%, 27.1%]
Sunitinib vs imatinib (Rankin)	32.0% [13.6%, 46.5%]	20.2% [6.9%, 33.5%]
Sunitinib vs imatinib (Demetri)*	35.5% Not done	23.7% Not done
Sunitinib vs imatinib (all)	29.5% [14.7%, 41.7%]	18.0% [8.5%, 27.4%]

*95% confidence intervals were not calculated for Demetri since the approximation of a binomial distribution by a normal distribution is not good for small numbers.

The submission presented, as clinically supportive, the protocol-specified efficacy results of Trial 1004 including time-to-progression (the primary outcome), PFS, overall survival, tumour response, and duration of performance status. At the first efficacy interim analysis time-to-progression showed statistical significance ($p<0.001$) in favour of sunitinib, exceeding the pre-specified significance ($p=0.0031$). After this analysis the protocol was amended to enable patients progressing on placebo to switch to sunitinib. The protocol provision for maintaining a 5% overall risk of false positive inference included only the time-to-progression analyses. These risk reduction calculations were made using the same events that contributed to the Kaplan-Meier PFS curves, not using events based on a time anchored analysis (such as progression at six months). Both the median PFS results and these results are derived from the Kaplan-Meier curves so the two should not be viewed as providing independent evidence.

The toxicity profiles of sunitinib and imatinib overall appeared generally similar although differing in some details. There were few systematic comparative data on the toxicity of patients who progress despite imatinib. The only randomized trial of imatinib failures was Trial 1004, comparing sunitinib to placebo. Valid toxicity data comparing imatinib continuation versus switching to sunitinib could only be obtained by a trial employing this design.

9. Clinical Claim

The submission claimed sunitinib offers significantly more efficacy than the main comparator and similar toxicity. The PBAC considered this claim was not adequately supported in the non-randomised comparison.

10. Economic Analysis

A preliminary across-trial comparison based economic evaluation was presented.

The submission acknowledged that on the basis of the claimed superior efficacy and similar toxicity, that the appropriate type of economic evaluation would be a cost-effectiveness analysis, but "in light of some uncertainty regarding the indirect comparison, due to the lack of imatinib data, the basis of the submission was one of cost minimisation, with the caveat that interchangeability is not appropriate, in light of the clear clinical place of each product. Accordingly the Sponsor sought listing on a cost minimisation basis.

The cost effectiveness evaluation was based on the yearly cost being less for sunitinib compared to imatinib. The resources included were drug costs and costs of managing adverse events. A cost-effectiveness analysis, based on Trial 1004, comparing sunitinib and placebo was not provided.

The submission claimed the across trial comparison based incremental cost/extra PFS year was dominant in the three analyses presented. A modelled economic evaluation was not presented.

See Recommendations and Reasons for PBAC view.

11. Estimated PBS Usage and Financial Implications

The submission claimed there would be cost savings to the PBS if listed.

12. Recommendation and Reasons

The PBAC agreed that 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 will bias later overall survival analyses towards the null.

However, the PBAC considered that the submission's cost-minimisation comparison with imatinib was inappropriate because it rests on the inadequately supported assumption that treatment with imatinib in eligible patients is no better than placebo. 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 is unknown.

Consequently the PBAC considered that the cost-minimisation approach taken by the submission was not sufficiently informative. The PBAC thus decided to defer consideration of this item pending the provision of further information to demonstrate that sunitinib is a cost effective treatment for gastro-intestinal tumour (GIST) after failure of imatinib.

The Committee indicated that a cost-effectiveness analysis against placebo for best supportive care in patients with GIST who have failed imatinib, would provide an appropriate basis for determining the cost-effectiveness of sunitinib.

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 to make.