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 advanced/metastatic renal cell carcinoma (RCC).

2. Background

At the March 2007 meeting, the PBAC deferred consideration of this item pending the provision of further economic analyses to demonstrate whether the treatment is acceptably cost effective. The Committee considered the estimated incremental cost per life year gained (LYG) over best supportive care (BSC) provided in the preliminary economic evaluation in the Pre-PBAC Response was unacceptably high and also uncertain. *(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. Requested Listing and PBAC's views

Authority required

For the treatment of advanced (unresectable or metastatic) renal cell carcinoma (RCC) in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

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

For PBAC's views see Recommendations and Reasons.

5. Clinical place for the proposed therapy

Renal cell carcinoma is a form of kidney cancer that arises from the cells of the renal tubule. Sunitinib would provide a treatment option for patients with advanced RCC.

6. Comparator

The submission nominated best supportive care without hormonal support (BSC/placebo) as the main comparator. This was previously suggested by PBAC. An analysis was also presented using BSC/hormonal support as a comparator.

7. Clinical trials

The re-submission presented new trial data. An updated progression free survival (PFS) analysis of Trial A618-1034 was presented and an indirect analysis of sunitinib (Trial A618-1034) versus BSC/hormonal support (MRC Renal Cancer Trial) using interferon-alfa as the common comparator.

Publication details for the presented trials are tabulated below.

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial used in Section B		
Trial A618-1034	Motzer R, Butson T, Tomczak P, et al. Sunitinib versus interferon-alfa in metastatic renal-cell carcinoma. Motzer, Update.	*NEJM* 2006, 356:115-24 ASCO presentation, 2007
MRC Renal Cancer Trial	MRC Renal Cancer Collaborators: Interferon-α and survival in renal cell carcinoma: Early results of a randomized controlled trial	*Lancet* 1999; 353:14-17

8. Results of Trials

The re-submission re-presented the progression free survival (PFS) results of Trial A618-1034 second interim analysis (60 weeks follow-up, 250 events: 232 progressions, 18 deaths) provided in the March 2007 submission. The re-submission updated these results in a subsequent unplanned PFS analysis (110 weeks follow-up, 434 events).

The second interim analysis of this trial demonstrated that treatment with sunitinib was associated with a significantly longer progression-free survival than treatment with interferon alfa (median progression-free survival sunitinib 47.3 weeks, interferon alfa 22.0 weeks, multivariate hazard ratio: 0.415, 95% CI 0.32 – 0.54).

The subsequent unplanned analysis at 110 weeks showed a median progression free survival with sunitinib of 47.7 weeks compared to 22.1 weeks for interferon-alfa, with a hazard ratio of 0.538 (95% CI 0.439- 0.658).

The MRC trial was terminated early due to the superiority of interferon-alfa over medroxyprogesterone acetate (MPA). The indirect comparison of sunitinib versus MPA demonstrated that sunitinib was associated with significantly longer progression free survival than MPA.

The PBAC considered an issue remained as to how intrinsically patient-relevant a PFS result is compared to an overall survival result, given that the large majority of PFS events are progression and that progression is usually asymptomatic. During the evaluation process it was suggested an informative alternative approach would be to extrapolate overall survival in a sensitivity analysis.

The re-submission did not present new toxicity data. The toxicity data from the previous submission were primarily the following: gastrointestinal (GI) and mucocutaneous events, neutropenia and thrombocytopenia, QT interval prolongation, decrease in left ventricular ejection fraction, seizures, hypothyroidism, and treatment related tumour haemorrhage.

Of particular concern to the PBAC was more recent evidence of cardiac side effects of ischemia and heart failure. A recent study[1] has suggested that patients taking sunitinib will require close cardiac monitoring. At the 2008 Genitourinary Cancers Symposium, lead author of the study Dr Melinda Telli (Stanford University School of Medicine, Palo

[1] Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. 2008 Genitourinary Cancers Symposium; February 16, 2008; San Francisco. Abstract 351, http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=54&abstractID=20439

Alto, CA) reported that 15% of patients taking sunitinib developed heart failure — more than the previously reported 8%. The researchers also emphasised that, contrary to previous findings, the effects were irreversible even after stopping therapy.

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

9. Clinical claim

The submission described sunitinib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care/placebo.

For PBAC's views see Recommendations and Reasons.

10. Economic analysis

A cost-effectiveness approach was presented.

The trial-based preliminary economic evaluation including drug costs showed an incremental cost of between $15,000 - $45,000 per progression free survival year gained compared to BSC/placebo.

The results of modelled economic evaluation (compared to BSC/placebo) were as follows:

- an incremental cost per extra progression free survival year gained of between $45,000-$75000;
- an incremental cost per life year gained of between $45,000 -$75,000; and
- an incremental cost per quality adjusted life year gained of between $75,000-$105,000.

The model was sensitive to the mortality risk difference between the without progression and with progression cohorts. The model was also sensitive the proportion of sunitinib patients who continue therapy post-progression.

11. Estimated PBS Usage and Financial Implications

The estimated number of patients/year was less than 10,000 per year at a financial cost/year to the PBS of between $10-30 million.

12. Recommendation and Reasons

The PBAC recognised the clinical need for additional treatments for this condition.

The PBAC had a number of concerns with the requested restriction wording, similar to those identified in the previous consideration of sunitinib for RCC in March 2007. Treatment should be limited to clear cell disease as this reflects the trial population and biological rationale for treatment. "Advanced" is an ambiguous descriptor of disease status and should be replaced by Stage IV disease, which, although it would encompass a slightly wider population with metastatic disease than included in the key trial, would be more acceptable. WHO performance status should be less than 2 at initiation.

The PBAC noted the comparator was no longer interferon-alfa and accepted BSC/placebo as the main comparator, as previously suggested by the Committee.

The primary efficacy data in support of listing sunitinib were derived from a randomised, head-to-head trial (Trial A618-1034) of sunitinib versus interferon alfa as first-line therapy in advanced/metastatic RCC. This trial was well conducted with blinded assessment of disease progression outcomes. The submission was based on the second interim analysis of this trial, which demonstrated that treatment with sunitinib is associated with a significantly longer progression-free survival than treatment with interferon alfa (median progression-free survival: sunitinib 47.3 weeks, interferon alfa 22.0 weeks; multivariate hazard ratio: 0.415, 95% CI 0.32 – 0.54). It was noted that overall survival did not reach the level of significance pre-specified in the trial for the interim analysis. The PBAC acknowledged that because patients that progressed were allowed to cross-over this would bias later overall survival analyses towards the null, thereby underestimating the likely true difference between the therapies.

The clinical relevance of progression-free survival has not been demonstrated in terms of improvements in symptoms or quality of life. Therefore, the benefit of sunitinib must be expressed in terms of the magnitude of the extrapolated survival gain. The PBAC considered the submission's Markov model, which extrapolated overall survival from progression-free survival, to be more informative than the direct extrapolation of overall survival data requested during evaluation, in this instance. This was for two main reasons:

- Trial A618-1034 was stopped early; and
- The majority of events in Trial A618-1034 were not deaths, but progressions (18 deaths vs. 232 progressions).

The direct extrapolation of overall survival, presented in the Pre-PBAC response, showed a two year survival gain which is implausible. 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 using on progression-free survival rates.

The PBAC noted that the model was sensitive to the proportion of patients continuing sunitinib post-progression.

The PBAC noted the increase in adverse events with sunitinib over BSC/placebo including GI and mucocutaneous events, neutropenia and thrombocytopenia, QT interval prolongation, decrease in left ventricular ejection fraction, seizures, hypothyroidism, and treatment related tumour haemorrhage. Of particular concern to the PBAC was more recent evidence of cardiac side effects of ischemia and heart failure. A recent study[2] has suggested that patients taking sunitinib will require close cardiac monitoring. At the 2008 Genitourinary Cancers Symposium, lead author of the study Dr Melinda Telli (Stanford University School of Medicine, Palo Alto, CA) reported that 15% of patients taking sunitinib developed heart failure — more than the previously reported 8%. The researchers also emphasised that, contrary to previous findings, the effects were irreversible even after stopping therapy.

The model presented in the submission inappropriately did not include costs or utilities for these adverse events.

[2] Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. 2008 Genitourinary Cancers Symposium; February 16, 2008; San Francisco. Abstract 351, http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=54&abstractID=20439

The PBAC considered the incremental cost effectiveness ratio of between $75,000 and $105,000per extra QALY gained to be unacceptably high and uncertain. The "predicted" survival gain of one year over a 10 year period was uncertain. While this was more reliable than the two years shown with direct extrapolation, predicting overall survival from progression-free survival is, in this case, not an externally validated method.

The treatment effect was likely to taper out in the first few years of treatment. The ICER increased per extra QALY gained if the treatment effect was tapered out over the first two years of the model. The ICER was also likely to be less favourable if sunitinib treatment continued after disease progression. In Trial A618-1034, patients could continue on sunitinib even after tumour progression occurred. A shorter time horizon will also make the ICER less favourable. Adverse events are not included in the model. This is especially important for heart failure.

Therefore, the PBAC rejected the submission, based on unacceptably high and uncertain cost effectiveness.

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 is working with the PBAC to resolve the issues raised.