PUBLIC SUMMARY DOCUMENT

Product: Sunitinib malate, capsules, 12.5 mg, 25 mg and 50 mg, Sutent®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The submission sought a Section 85 Authority Required listing for the treatment of advanced renal cell carcinoma (RCC).

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Sunitinib malate 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

Authority Required – Section 85
For the treatment of advanced renal cell carcinoma.

In addition, the submission presented analyses corresponding to listings restricted by a PBS continuation rule requiring tumour response at 12 weeks (after 2 cycles of treatment). The first analysis requires patients be "stable or better" using RECIST criteria, censoring patients who do not meet these requirements. The second, "restricted listing #2 analysis," censors patients if they do not show tumour response (partial or complete) at 12 weeks (after 2 cycles).

See Recommendations and Reasons for PBAC's view.

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. Currently, only interferon alfa is registered in Australia for the management of metastatic RCC but is not PBS listed for this indication. Sunitinib could be used as an alternative treatment for patients with advanced RCC.

6. Comparator

The submission nominated best supportive care (BSC) +/- interferon alfa-2a as the main comparator. The submission also nominated sorafenib as a supplementary comparator.

The PBAC did not accept that best supportive care (BSC) +/- interferon alfa is the appropriate comparator.

See Recommendations and Reasons for PBAC's views.

7. Clinical Trials

For the primary comparator (BSC + interferon-alfa), the submission presented interim analysis of one Phase III open head-to-head trial (Trial A618-1034) of sunitinib versus interferon-alfa as first line therapy in advanced/metastatic RCC and three supportive single arm studies (Study RTKC-0511-014, Study A618-1006, and Study A618-1039) as second line therapy in cytokine-refractory RCC and one supportive safety (QTc) study (Study A618-1005). For the supplementary comparator, sorafenib, the submission presented two trials (Ratain/2006, an open-label PHASE II study and TARGETS a PHASE III secondline study vs placebo). The main evidence was provided by Trial A618-1034. The three supportive studies for the primary comparator were all small, single-arm studies in patients having failed first line therapy. Because of limited data from the sorafenib trials, the supplementary comparison was only descriptive.

One of these studies had been published at the time of the submission, as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Ratain	Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients With Metastatic Renal Cell Carcinoma	Journal of Clinical Oncology, Vol 24, No 16 (June 1), 2006: pp. 2505-2512

8. Results of Trials

The results of the time-to-first event analyses, Cox proportional hazards models (CPH), and post hoc "restricted listing #2 analysis" of progression-free survival (PFS) and overall survival (OS) from Trial A618-1034 were presented. There were no data in the submission to determine if progression increased symptoms, worsened quality-of-life, or shortened survival.

The PBAC agreed that 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 was associated with a significantly longer time to progression than treatment with interferon alfa. 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, interpretation of future estimates of overall survival benefit would be difficult because of an expected tendency to the null underestimating the likely true difference between the therapies. The trial is on-going.

The PBAC noted sunitinib demonstrated more serious adverse events, more treatment related serious adverse events, and more adverse events with a frequency of 10% or more or a ratio of 2 or more compared to interferon-alfa (see table below). The toxicity differences with interferon-alfa were substantial. Of particular concern were in the incidence of thrombocytopaenia and neutropaenia in the sunitinib arm.

9. Clinical Claim

The clinical claim made in the submission is that sunitinib is significantly more effective than the main comparator, interferon alfa, but has more toxicity.

See Recommendations and Reasons for the PBAC's view.

10. Economic Analysis

A preliminary trial-based economic evaluation was presented. The choice of the cost-effectiveness approach was considered valid. The resources included were drug costs and adverse event management costs. The overall comparative costs and outcomes for the base case analysis and the restricted listing #2 analysis and the incremental costs and outcomes are summarised in the following tables.

The trial-based (over interferon-alfa) incremental cost/extra PFS-year gained was between $75,000 and $105,000. The trial-based incremental cost/extra life-year gained was between $105,000 and $200,000.

A modelled economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The cost to the PBS was estimated to be $10 to 30 million per year in the first four years of listing.

12. Recommendation and Reasons

Although sympathetic of the clinical need for additional treatments for this condition and encouraged by the benefits shown in the submitted clinical trials, the PBAC deferred consideration of this item pending the provision of further economic analyses to demonstrate whether the treatment is acceptably cost effective.

The PBAC had a number of concerns with the requested restriction wording. 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. A continuation rule based on restricting treatment to only those who are responders (using RECIST criteria) would not be appropriate because it is neither clinically sustainable nor consistent with the logic of the submission's argument where clinical benefit equals no progression. For this reason, the PBAC did not consider those aspects of the submission which reported clinical and economic results based on sub-group analyses corresponding to continuation rule of responders only ("Restricted listings #2").

The PBAC did not accept that best supportive care (BSC) +/- interferon alfa is the appropriate comparator. The Committee considered that although the survey presented in the submission suggests that some oncologists use interferon alfa in a proportion of patients, this

is not the norm and furthermore, interferon alfa is not PBS subsidised and has not been assessed as being cost-effective for use in RCC. Thus, although a comparison with interferon alfa may be reasonable on the grounds that it would be substituted to some extent, such a comparison alone would not assist the PBAC in assessing the cost effectiveness of sunitinib, i.e. the cost-effectiveness of interferon alfa would also need to be established as a pre-requisite to enabling a PBAC judgement about the cost-effectiveness of sunitinib in relation to interferon alfa. The PBAC considered that BSC alone is the more informative comparator and accepted that, as in the Pre-PBAC Response, this would involve an indirect comparison of randomised trials with interferon alfa as the common reference.

The PBAC agreed that the primary efficacy data in support of listing sunitinib were derived from a randomised, head-to-head Phase III 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 time to progression than treatment with interferon alfa (median progression-free survival sunitinib 47.3 weeks, interferon alfa 22.0 weeks, multivariate hazard ratio: 0.37, 95% CI 0.28 – 0.48). 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, interpretation of future estimates of overall survival benefit would be difficult because of an expected tendency to the null underestimating the likely true difference between the therapies.

The submission reasonably argued there is an association between progression-free survival and overall survival on the basis that, although only 7% of progressions are deaths, it can be shown that death was more likely in patients with tumour progression than those without tumour progression. However, the PBAC considered that the demonstration of this association alone does not provide sufficient evidence to enable a confident prediction of the extent of survival gain based on the estimated difference in time to progression and that survival data is and should be used in the economic analyses directly.

The PBAC agreed with the ESC that sunitinib is associated with more toxicity than interferon alfa in some patients. Of particular concern were the incidence of thrombocytopenia and neutropenia in the sunitinib arm of the key study.

The PBAC had concerns about the additional cost of therapy and consequently worse cost-effectiveness, if patients are treated with sunitinib on a continuous daily basis at a dose of 37.5 mg and a continuous daily basis at a dose of 50 mg, rather than the intermittent dosing schedule in the submission. This was thought to be a possibility because clinicians would be concerned that patients may relapse when therapy is suspended for the 2 weeks break in treatment. The PBAC also considered it unlikely that, in clinical practice, patients would discontinue treatment upon progression.

The Committee considered the estimated incremental cost per life year gained over BSC provided in the preliminary economic evaluation in the Pre-PBAC Response was unacceptably high at between $75,000 and $105,000 and also uncertain. The PBAC considered that that the “Responder analysis #1”, for a restriction allowing continuation of

sunitinib in patients with stable disease or better, was less informative because applying such a continuation rule was not clinically sustainable and this analysis relied on inadequately supported post-trial sub-group analyses. The PBAC noted that a modelled economic analysis had not been presented and deferred the submission to allow such an analysis to be provided by the appropriate submission deadline to allow full evaluation by the PES and consideration by the ESC before it is reconsidered by the PBAC. The longer-term survival with BSC can be sourced from epidemiological studies stratified by relevant prognostic criteria. Quality-adjustment of the modelled survival gains would be appropriate. The PBAC also requested that appropriate sensitivity analyses be conducted to investigate the impact on the cost-effectiveness of treatment of varying the sunitinib dose regimen, in particular replacing the intermittent dose schedule proposed in the submission with a continuous dosing schedule, and of treating to death rather than to a defined "stopping" point.

Any submission should also discuss the basis upon which the PBAC should assess the plausibility of any particular estimate in the range of variations examined in these analyses.

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 for sunitinib in RCC.