

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Sunitinib malate, capsules, 12.5 mg, 25 mg and 50 mg (base), Sutent<sup>®</sup>

**Sponsor:** Pfizer Australia Pty Ltd

**Date of PBAC Consideration:** July 2008

### **1. Purpose of Application**

To seek an Authority required listing for the treatment of advanced/metastatic renal cell carcinoma (RCC).

To address key uncertainties arising in the evaluation and assessment from the March 2008 PBAC submission.

### **2. Background**

At the March 2007 meeting, the PBAC deferred consideration of an authority required listing for renal cell carcinoma 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 over best supportive care (BSC) provided in the preliminary economic evaluation in the Pre-PBAC Response was unacceptably high and also uncertain. (*See PBAC Public Summary Document - March 2007*)

At the March 2008 meeting, the PBAC rejected the re-submission based on unacceptably high and uncertain cost effectiveness. (*See PBAC Public Summary Document - March 2008*)

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.

### **3. Registration Status**

Sunitinib malate was registered by the TGA on 14 September 2006 for the treatment of:

- Advanced renal cell carcinoma;
- 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 advanced (unresectable or metastatic) renal cell carcinoma (RCC) in patients with an ECOG performance status of 0 or 1.

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

*For PBAC's view, see Recommendation 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 placebo (best supportive care) as the main comparator, which had been previously accepted by the PBAC.

## **7. Clinical Trials**

Reported in the March 2008 PBAC Public Summary Document.

## **8. Results of Trials**

The primary amendments in this submission compared with the March 2008 submission were:

- A decrease in effective price; and
- Correction of the pre- and post progression mortality rates from the previous economic analysis which were noted as underestimating survival.

The submission aimed to address three key issues identified at the March 2008 meeting as uncertain:

- Progression free survival – treatment effect may taper out in the first few years of treatment;
- Survival mortality rate – was considered in the previous submission to be subject to bias; and
- Adverse events, in particular heart failure.

The submission provided Australia data (from EMBRACE) to address the cardiovascular safety issue and sensitivity analyses incorporate the possible impact of heart failure. The submission also provided a full abstract of the study by Telli et al, and added in the heart failure rates from this study, from Chu et al 2007, as well as from a paper published by Khakoo (2008).

The submission presented updated survival data from a key efficacy study (A618-1034), included in the previous submission, to address the concern that the treatment effect might cease or taper off beyond the trial period and performed a sensitivity analysis that used the calculated hazard ratio (HR) for sunitinib versus interferon-alfa for years 0-2 only, tapering off thereafter so that the hazard ratio reached 1.0 by year 6, with the HR of 1.0 remaining constant thereafter for the duration of the 10 year model.

The submission sought to address the uncertainty surrounding survival by application of a “Landmark Analysis” to generate mortality rates in the post-progression and non-progression health states to avoid “*guarantee-time bias*” in the survival estimates.

## **9. Clinical Claim**

Reported in the March 2008 PBAC Public Summary Document.

## **10. Economic Analysis**

The submission stated that the economic model previously presented to the PBAC was essentially unchanged other than addressing areas of uncertainty surrounding the cost-

effectiveness ratio. All areas of uncertainty previously identified by the PBAC in March 2008 were addressed by additional analyses undertaken in the submission.

The submission used the Markov model for the modelled economic analysis, which was amended by a reduction in the dispensed price maximum quantity (DPMQ), and used the mortality rates from the 10-weeks Landmark Analysis (10-weeks post randomisation was selected because it was the time of the first radio-imaging scan after the first complete dose cycle were assessed for progression; sensitivity analyses also undertaken for 8-week and 12-week landmark). The submission estimated the incremental cost-effectiveness ratio to be in the range of \$45,000 – 75,000 per quality adjusted life year (QALY).

*For PBAC's view, see Recommendation and Reasons.*

## **11. Estimated PBS Usage and Financial Implications**

Reported in the March 2008 Public Summary Document.

## **12. Recommendation and Reasons**

The PBAC recommended the listing of sunitinib on the PBS for the treatment of certain patients with renal cell carcinoma on the basis of acceptable cost-effectiveness compared with best supportive care at the new price proposed. As previously, the PBAC considered that treatment should be limited to Stage IV, clear cell variant renal cell carcinoma. Patients should also meet the Memorial Sloan Kettering Cancer Centre (MSKCC) low to intermediate risk group criteria, have a WHO performance status of 2 or less and treatment should be as sole PBS-subsidised therapy. The continuation criteria should be defined by the RECIST criteria as this would better reflect the population in the clinical trials.

The PBAC noted that the submission presented an amended modelled evaluation in which compared to the previous model: the price was reduced (to be achieved via a risk sharing agreement) and pre- and post-progression mortality rates were derived from a Landmark analysis which was conducted to avoid guarantee-time bias in the survival estimates. The following were explored in sensitivity analyses to address previous concerns of the PBAC regarding emerging data on congestive cardiac failure: 7.3% of patients were allowed to continue the drug despite disease progression and the percentage of patients who incur hospitalisation costs due to heart failure was increased from 17.6% to 21.92%. The revised estimated ICER in the range of \$45,000 – 75,000 per QALY was considered high but robust and acceptable in an area of high clinical need where no effective alternative treatments are currently available.

### ***Recommendation***

SUNITINIB MALATE, capsules, 12.5 mg, 25 mg and 50 mg (base)

Restriction:

#### Authority required

Initial treatment, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who meets the Memorial Sloan Kettering Cancer Centre (MSKCC) low to intermediate risk group and has a WHO performance status of 2 or less.

NOTE: No applications for increased maximum quantities and/or repeats will be authorised.

Maximum quantity: 28  
Repeats: 1

Authority required

Continuing treatment beyond 3 months, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who has previously been issued with an authority prescription for sunitinib and who has stable or responding disease according to RECIST criteria.

NOTE:

RECIST Criteria is defined as follows:

Complete response (CR) is disappearance of all target lesions.

Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.

Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.

Stable disease (SD) is small changes that do not meet above criteria.

Authority required (grandfather)

Initial treatment, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who was receiving treatment with sunitinib prior to (insert LISTING DATE).

Maximum quantity: 28  
Repeats: 3

**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**

Pfizer Australia welcomes the positive recommendation of the PBAC and looks forward to finalising the listing of sunitinib on the PBS for the treatment of stage IV clear cell variant renal cell carcinoma.