PUBLIC SUMMARY DOCUMENT
Product: Sorafenib tosylate, tablet, 200 mg (base), Nexavar®
Sponsor: Bayer Australia Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application
The submission sought an Authority Required listing for initial and continuing treatment of advanced renal cell carcinoma (RCC) in patients who meet certain criteria.

2. Background
At the November 2006 meeting, the PBAC rejected a submission for sorafenib based on uncertainty of the extent of gain in overall survival, and the resulting high and uncertain cost-effectiveness ratio. Overall, the PBAC accepted that there is a clinical need for additional treatment options for the management of renal cell carcinoma but that the data presented in the submission did not present, with an adequate degree of certainty, the extent of benefit that would be realised should sorafenib be listed on the PBS.

3. Registration Status
Sorafenib was TGA registered for the treatment of patients with advanced renal cell carcinoma on 27 September 2006.

4. Listing Requested and PBAC's View
Authority Required
Initial treatment of advanced (unresectable or metastatic) renal cell carcinoma in patients with WHO performance status 2 or less.
Continuing treatment of advanced renal cell carcinoma where the patient is not experiencing (or is free of) disease progression.
Disease progression is defined as a 20% increase in the sum of the longest diameter of target lesions using X-ray, CT or MRI.

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

See Recommendations and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy
Sorafenib is expected to be used alongside the current practice of best supportive care and in the minority of cases, it may replace immunotherapy or chemotherapy in the treatment of advanced renal cell carcinoma.

6. Comparator
The submission nominated placebo for best supportive care (BSC) as the main comparator. Best supportive care consists of the use of pain medication, radiotherapy and other supportive therapies. The PBAC had previously agreed that this is the appropriate comparator.

The submission also nominated sunitinib as a secondary comparator. Although data from trials located with a common comparator (interferon-alfa) were presented, no comparison of the trials was provided, as it was not considered appropriate by the sponsor.

7. Clinical Trials

The re-submission presented an updated analysis of overall survival from Trial 11213. Trial 11213 enrolled patients who had advanced RCC and had previously been treated with one systemic therapy after which they experienced disease progression. Thus, study 11213 provided evidence of the use of sorafenib as second line therapy where other therapies have failed.

Two trials for the comparison of sorafenib versus sunitinib using interferon as a common comparator were also presented, Trial 11848, comparing sorafenib and interferon-alfa, and Motzer et al. 2007 comparing sunitinib and interferon alfa.

Trials published at the time of the re-submission are presented in the table below.

Trial/First author	Protocol title/Publication title	Publication citation
Bukowski et al, 2007	Effects of sorafenib on symptoms and quality of life: Results from a large randomized placebo-controlled study in renal cancer.	American Journal of Clinical Oncology: Cancer Clinical Trials 30(3): 220-227
Escudier et al, 2007	Sorafenib in advanced clear-cell renal-cell carcinoma.	The New England Journal of Medicine 356(2): 125-134.
Lamuraglia et al, 2006	To predict progression-free survival and overall survival in metastatic renal cancer treated with sorafenib: Pilot study using dynamic contrast-enhanced Doppler ultrasound.	European Journal of Cancer 42(15): 2472-2479.
Motzer et al, 2007	Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.	The New England Journal of Medicine 356(2): 115-24.

8. Results of Trials

The result of the overall survival analysis comparing sorafenib and BSC/placebo is unchanged from the previous submission, i.e. no statistical significance was demonstrated. However, ,progression-free survival reached significance. The results to 31 May 2005, before cross-over, are the most relevant (Hazard Ratio (HR) = 0.71). The overall survival (OS) results did not reach statistical significance as pre-specified by the trial protocol.

The key results are summarised in the table below.

Overall survival results of Trial 11213

	Level of statistical significance		Other analyses (95% CI)
	Observed	Needed*	
Current submission **8 September 2006 of overall survival with 216 BSC/placebo patients crossed over to sorafenib – 561 deaths (deaths by randomized treatment: not reported)**			
Comparison of time-to-first event by 2-sided stratified log rank test	P=0.146	Not provided but must be P<0.05	HR = 0.88 (0.74, 1.04)
Same as above but with all placebo patients censored at 30 June 2006	Not included in the alpha spending plan		HR=0.78 (0.62, 0.97)
Previous submission			

31 May 2005 of overall survival – 220 deaths (sorafenib 97, BSC/placebo 123)			
Comparison of time-to-event by 2-sided stratified log rank test	P=0.018	P=0.0005	HR = 0.71 (0.54, 0.94)**
Previous submission **30 November 2005 of overall survival - 367 deaths (sorafenib 171, BSC/placebo 196)**			
Comparison of time-to-event by 2-sided stratified log rank test	P=0.015	P=0.0094	HR=0.77 (0.63, 0.95)

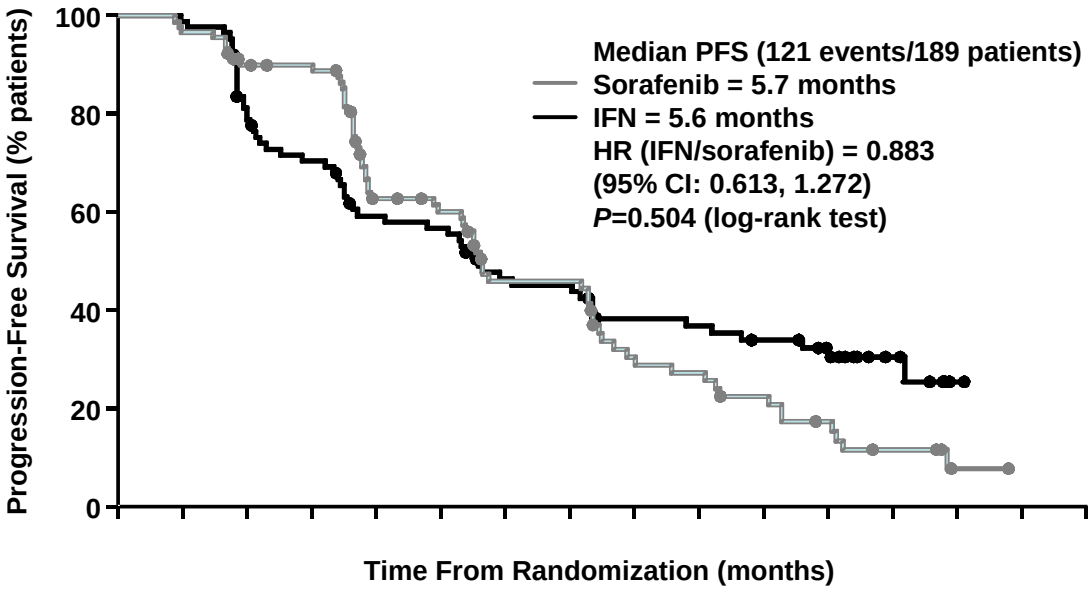
Notes: HR=hazard ratio.

* Needed significance levels for interim analyses are dependent on the exact number of events at the time of the analysis constrained by the overall apportionment of the alpha which here was 0.01 for progression free survival (PFS) and 0.04 for overall survival. The protocol and statistical analysis plan provided for one interim and one final OS analysis plus one PFS analysis. After the PFS analysis of 28 January 2005, a decision was made in April 2005 to terminate randomized assignment and allow crossover, and plan for three OS analyses: The first on 31 May 2005, a second on 30 November, and a final at 540 deaths which turned out to be on 8 September 2006

** The HR of 0.71 is reported in the current submission, whereas 0.72 was reported in the previous submission. The discrepancy is explained by the current database being more complete and up to date.

Trial 11848 was an open-label comparison of sorafenib and interferon-alfa in 189 patients with previously untreated RCC. The primary outcome was progression-free survival by independent review. Upon reaching progression, sorafenib patients underwent a dose increase and interferon-alfa patients switched to sorafenib. There were 121 PFS events. 43 patients assigned to sorafenib had their dose increased and 50 patients assigned to interferon-alfa were switched to sorafenib. The Kaplan-Meier curves are shown below with a log-rank test of p=0.504. Median PFS was 5.9 months for sorafenib compared to 5.6 months for interferon-alfa.

Trial 11848 Kaplan-Meier estimates for progression-free survival (by independent assessment)



Patients at risk					
Sorafenib	97	75	30	16	4
IFN	92	57	34	24	7

The above K-M curve suggested that sorafenib and interferon-alfa have similar progression free survival. In addition, the PBAC noted a Cochrane review of interferon-alfa for advanced RCC (Coppin et al. 2004) which concluded that interferon-alfa provided a modest overall survival benefit compared to other commonly used treatments (overall survival HR=0.74 (95% CI: 0.63 to 0.88); and weighted average median improvement in survival was 3.8 months). The treatment effect for overall survival for interferon vs. BSC as estimated in the Cochrane review was of similar magnitude to the treatment effect for overall survival being claimed in this submission for sorafenib vs. BSC.

9. Clinical Claim

The re-submission described sorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC/placebo.

See Recommendations and Reasons for PBAC's view.

10. Economic Analysis

A new modelled economic evaluation was presented which, compared with the model in the previous submission, was 5 instead of 11 years in duration and modeled two health states (alive and dead) instead of three (progression-free, disease progression and dead).

The model used a more patient relevant outcome, survival, and thus avoided the problem of limited evidence on the patient relevance of "progression". However, the model relied on an outcome, overall survival, the result of which failed to attain statistical significance in the trial. Drivers of the model were the treatment effect and its duration, the duration of sorafenib usage, and the utility assumed beyond the trial duration.

The economic evaluation produced an incremental cost per extra QALY gained in the range of $45,000 to $75,000.

11. Estimated PBS Usage and Financial Implications

The estimated likely number of patients per year was less than 10,000 in Year 1 at a financial cost per year to the PBS of between $10-$30 million in Year 1.

12. Recommendation and Reasons

The PBAC accepted that there is a clinical need for additional treatment options for the management of renal cell carcinoma.

The requested listing for first line treatment was not supported by the pivotal trial evidence presented in the submission, Trial 11213, which is in second line. Although the re-submission implies that a first line listing is appropriate because the subgroup analysis of patients without prior cytokine therapy showed improved survival compared to those with such prior therapy, the subgroup analysis cannot add to this inference because the overall survival analysis for the trial was not statistically significant, the subgroup analysis was not pre-specified and the patient group was not adequately defined. The only evidence supporting a treatment setting for sorafenib was in patients in whom cytokine therapy had failed, although these therapies are not currently PBS listed. Even in this setting, the evidence being relied on would be progression-free survival, not overall survival.

The only first-line trial available (Trial 11848, which was open-label) showed no benefit in progression-free survival or overall survival. The PBAC therefore considered a PBS listing of sorafenib for first line use would not be appropriate.

The PBAC agreed that the data in Trial 11213 suggests that treatment with sorafenib to improve progression free survival, however considered that the clinical importance of this gain had not been demonstrated in the submission, either in terms of symptoms of renal cell carcinoma or as a surrogate to predict future survival gain. Although in clinical practice there may be a select population in whom there is a survival benefit, the 4 month survival benefit claimed in the submission remained uncertain. The Committee noted the influence that the cross over from placebo to sorafenib treatment in the pivotal trial (Trial 11213), had on the ability of the submission to demonstrate efficacy in terms of the extent of overall survival gain compared to placebo.

The PBAC noted that only 9.5% of patients achieved a partial response to sorafenib as compared to 1.8% for placebo, in the comparison of RECIST categories determined by the investigator. The clinical rationale for patients not achieving a partial response was unknown.

The PBAC noted that sorafenib is associated with a variety of adverse events and laboratory findings including dermatologic and gastrointestinal events, hypertension, sensory neuropathy, and neutropenia. Additionally, a six-fold increase in cardiac ischaemia/infarction was found in Trial 11213 for sorafenib treated patients compared to placebo. Diarrhoea, rash, fatigue, hand-foot syndrome, alopecia and nausea were reported in >20% patients.

While the modelled economic evaluation was technically sound in terms of the decision to use overall survival rather than progression-free survival, issues of uncertainty remained from the extrapolation of the overall survival data from the clinical evidence. In the previous submission considered in November 2006, the key concern raised by the modelled economic evaluation related to the time horizon where nine to twelve months' worth of data were extrapolated to eleven years. The model structure in the current re-submission had improved, with a shorter time horizon of 5 years and a price reduction of DPMQ. However, these changes were not enough to offset the clinical uncertainties and the ICERs remained unacceptably high.

The PBAC therefore rejected the submission based on an unacceptably high and uncertain cost effectiveness ratio. There is high clinical uncertainty associated with the claimed survival advantage, but the place of sorafenib in the treatment algorithm is uncertain.

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

Sponsor chose not to make a comment.