PUBLIC SUMMARY DOCUMENT

Product: Sorafenib Tosylate, tablet, 200 mg (base), Nexavar®

Sponsor: Bayer Australia Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission requested an Authority Required listing for sorafenib for initial and continuing treatment of advanced renal cell carcinoma in patients who meet certain criteria.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Sorafanib was registered by the TGA on 25 September 2006 for the treatment of patients with advanced renal cell carcinoma.

4. Listing Requested and PBAC's View

Authority required

Initial (up to 3 months) treatment of advanced (unresectable or metastatic) renal cell carcinoma in patients with WHO performance status of 2 or less.

Continuing treatment of advanced renal cell carcinoma (beyond 3 months) in patients with stable disease or responding disease (according to RECIST criteria).

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Renal cell carcinoma can often be cured if it is diagnosed and treated when still localised to the kidney. When distant metastases are present, disease-free survival is poor.

Palliative treatment is usually employed to help patients with advanced renal cell carcinoma (kidney cancer) and help patients live without pain or distress.

Currently, only a small percentage of patients with advanced renal cell carcinoma receive any active immunotherapy or chemotherapy, with the most commonly used agent being interferon alfa. Patients may receive pain medication and/or radiotherapy for symptom control (best supportive care).

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.

6. Comparator

The submission nominated placebo for best supportive care (BSC) as the main comparator. The PBAC agreed that this is the appropriate comparator.

For further information on the PBAC's views regarding the comparator see Recommendation and Reasons.

7. Clinical Trials

The submission provided a comparison between sorafenib and placebo in two randomized trials. Trial 11213 was a placebo controlled trial of 903 patients (pivotal trial), and Ratain/2006 was a small randomized discontinuation trial of 65 patients who had stable disease at the end of an open run-in period of 12 weeks on sorafenib.

These trials had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
Ratain et al	Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma.	Journal of clinical oncology Jun 1 2006, 24 (16) p2505-12.
Dhanda et al.	Comparison of quality of life and symptoms in kidney cancer patients receiving sorafenib versus placebo.	J. Clin Oncol 2006; 24 (18Suppl): Abstract 4534. Am Soc Clin Oncol, Asco, Orlando USA, May 2006
Eisen et al.	Trial of sorafenib in advanced renal cell carcinoma (RCC): impact of cross-over on survival"	J. Clin Oncol 2006; 24 (18Suppl): Abstract 4524. Am Soc Clin Oncol, Asco, Atlanta, USA, June 2006
Gao et al.	Cost-effectiveness of sorafenib versus best supportive care in advanced renal cell carcinoma.	J. Clin Oncol 2006; 24 (18Suppl): Abstract 4604 Am Soc Clin Oncol, Asco, Orlando USA, May 2006
Escudier et al.	Randomised phase III trial of the multikinase inhibitor sorafenib (bay 43-9006) in patients wit advanced renal cell carcinoma (RCC).	Eur Urol. 2006; Suppl 5 (2): 287.
Escudier et al.	Randomised phase III trial of the multikinase inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC).	21st Annual Congress of the European-Association-of-Urology Paris, FRANCE April 05 -05, 2006; 20060405
Stehler et al.	Randomized phase III trial of the multi-kinase inhibitor sorafenib (bay 43-9006) in patients with advanced renal cell carcinoma (RCC).	Dtsch Krebskongress, Berlin, Germany, March 2006: Abstract
Escudier et al.	Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC).	J.Clin.Oncol. 2005; 23(16Suppl), Abstract 4510, 2005. Am Soc Clin Oncol, Asco, Orlando USA, May 2005
Ratain et al.	Final findings from a phase II, placebo-controlled, randomized discontinuation trial of sorafenib (bay 43-9006) in patients with advanced renal cell carcinaoma.	J.Clin.Oncol. 2005; 23(16Suppl), Abstract 4544, 2005 Am Soc Clin Oncol, Asco, Orlando USA, May 2005: (2005)
Escudier et al.	Randomized phase III trial of the multi-kinase inhibitor sorafenib (bay 43-9006)	EJC 2005. Suppl 3 (2): 226 Abstr 794.

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	in patients with advanced renal cell carcinoma (RCC).	
Eisen et al.	Preliminary antitumor activity in metastatic renal cell carcinoma in a phase in randomized discontinuation trial.	Symp Targeted Anticancer Ther, Mar 2005, Amsterdam
Escudier et al.	Randomized phase III trial of the raf kinase and vegfr inhibitor sorafenib (bay 43-9006) in patients with advanced renal cell carcinoma (RCC).	J Clin Oncol 23 (16 PT 2): 1093 205
Ratain et al.	Preliminary antitumor activity of BAY 43-9006 in metastatic renal cell carcinoma and other advanced refractory solid tumors in a phase II randomized discontinuation trial (RDT).	J.Clin.Oncol.. 2004; 22 (14 Suppl): Abstract 4501. Am Soc Clin Oncol, Asco, Orlando USA, May 2004
Ratain et al.	A phase II study of BAY 43-9006 using the randomized discontinuation design in patients with advanced refractory cancer.	Clin.Cancer Res. 2003; 9(16), 6265S-6266S.

8. Results of Trials

The results of the key trial on progression-free survival, overall survival, Response Evaluation Criteria In Solid Tumours (RECIST) categories and disease control rate (proportion of patients with responding or stable disease), and Health Related Quality of Life (HRQOL) measures are summarised in the tables below.

Progression-free survival results in Trial 11213 (as of 28 January 2005)

Analysis	Event rate (progression or death) Sorafenib vs placebo	HR (95% CI) p value (log rank)
Progression-free survival	147/384 (38.3%) vs 195/385 (50.6%)	0.44 (0.35, 0.55) P<0.000001 (allocated alfa: 0.01)

Note: An event is either progression or death prior to progression, so progression-free survival is the inverse of the event rates, i.e., 61.7% for sorafenib and 49.4% for placebo.

There was a statistically significant improvement representing a 56% reduction in the hazard ratio of progression free survival (PFS) over placebo. This corresponds to a median PFS of 167 days for sorafenib compared to 84 days for placebo. The submission also presented the results for PFS as of 31 May 2005 as assessed by the investigators rather than by independent review.

Overall survival results in Trial 11213 (as of 31 May 2005)

Analysis	Event rate (death) Sorafenib vs placebo	HR (95% CI) p value (log rank)
Overall survival	97/451 (21.5%) vs 123/452 (27.2%)	0.72 (0.55, 0.95) P=0.018 (p=0.009 needed for early stopping)

Note: An event is death, so overall survival is the inverse of the event rates, i.e., 78.5% for sorafenib and 72.8% for placebo.

From this date, 31 May 2005, the trial was unblinded and placebo patients offered sorafenib, so no subsequent analysis of overall survival would be uncertain and potentially underestimate the value of therapy. *See Recommendation and Reasons for the PBAC's view.*

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 ischemia/infarction was found in Trial 11213.

9. Clinical Claim

The submission claimed that sorafenib demonstrated benefits in survival and in progression-free survival but also had more toxicity than best supportive care (BSC). The PBAC agreed with this claim but considered that the extent of benefit for overall survival and Health Related Quality of Life (HRQOL) to be unclear.

See Recommendation and Reasons for the PBAC's view.

10. Economic Analysis

A preliminary economic evaluation was presented. The resources included were drug costs, monitoring, and treatment of adverse events.

The submission estimated the base case modelled incremental discounted cost/discounted extra life year gained or QALY to be in the range $15,000 - $45,000.

In its Pre-PBAC Response, the sponsor claimed that the base case cost per extra QALY gained at 5 months as presented in the clinical secondary analysis was estimated to be in the range $45,000 - $75,000.

The PBAC considered that the conservative base case incremental cost-effective ratio (ICER) estimate in the range $45,000 - $75,000 to be high and uncertain, with the possibility that the ICER being greater than $150,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be < 10,000 in Year 4 and the financial cost/year to the PBS was estimated to be in the range $10 – 30 million in Year 4.

The PBAC considered that the estimates of usage may result in net costs ≥ $10 million/year to the PBS in the first year of listing at least.

12. Recommendation and Reasons

The PBAC agreed that placebo for best supportive care to be the appropriate comparator and noted, given the shortage of treatment options for renal cell carcinoma, that some patients are being treated with newer agents under clinical trial conditions. The PBAC accepted that there is a clinical need for additional treatment options in this group of patients.

The Committee agreed that the data presented in the submission demonstrated that sorafenib is associated with an overall survival gain, but the extent of this gain is uncertain. The Committee noted the influence that the cross over 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 Committee considered that the

extent of overall survival gain is not quantifiable, due to the corruption of the data resulting from the need to cross patients over to active treatment in the clinical trial. The sponsor's comments in its Pre-PBAC Response regarding this issue was noted, including the pre-specified secondary analysis that was conducted to understand the impact of the cross-over on overall survival in placebo patients. The Committee felt that the sponsor's estimated 5 months overall survival gain of sorafenib over placebo, remained debatable, and noted that statistical significance had not been reached.

The PBAC agreed that the data supports that sorafenib improves progression free survival, however considered that the clinical relevance of this gain had not been demonstrated in the submission, either in terms of symptoms of renal cell carcinoma or prediction of survival. The PBAC noted that once patients had progressed in Trial 11213, they were only followed up for vital status and that no data directly describing the relation of progression to symptoms were presented.

The PBAC noted that in the pivotal trial, 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 is unknown. There was no statistically significant difference in patients achieving a complete response and 73.8% of patients achieved stable disease with sorafenib compared with 52.9% with placebo. All three categories were included in the requested restriction.

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 ischemia/infarction was found in Trial 11213. Diarrhoea, rash, fatigue, hand-foot syndrome, alopecia and nausea were reported in >20% patients.

The key concern raised by the modelled economic evaluation related to the time horizon. The assumptions resulted in the model predicting an incremental survival in excess of the survival shown in the results of the clinical trial.

The PBAC considered that the conservative base case incremental cost-effective ratio (ICER) estimate in the range $45,000 - $75,000 to be high and uncertain, with the possibility of the ICER being greater than $150,000.

The PBAC agreed that the revised estimates of usage may be an underestimate due to uncertainties relating to prevalence and possible increased rate of referral resulting from the availability of subsidised sorafenib. The sponsor's pre-PBAC response regarding expected uptake was noted by the Committee, with the final estimate of total cost to government to be in the range $10 - $30 million in year 4 of PBS listing.

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. The Committee considered that the conservative base case ICER estimate in the range $45,000 - $75,000 to be high and uncertain, with the possibility of the ICER being greater than $150,000. The PBAC therefore rejected the

submission on the basis of uncertainty of the extent of gain in overall survival, and the resulting high and uncertain cost-effectiveness ratio.

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

Bayer Australia Ltd continues to be concerned that the current treatment options for advanced renal cell carcinoma are limited and is committed to securing a PBS listing for sorafenib. The sponsor is planning to resubmit an application.

In the meantime, Bayer Australia Ltd suggests that patients with advanced renal cell carcinoma speak to their clinicians about treatment options.