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

1. Purpose of Application

The submission sought an Authority required listing for sorafenib for the treatment of advanced hepatocellular carcinoma in patients with unresectable disease.

2. Background

Sorafenib for this indication had not previously been considered by the PBAC.

3. Registration Status

Sorafenib was TGA registered on 25 February 2008 for:
Treatment of patients with advanced hepatocellular carcinoma.

Sorafenib was TGA registered on 27 September 2006 for:
Treatment of patients with advanced renal cell carcinoma.

4. Listing Requested and PBAC's View

Authority required
Initial treatment of advanced hepatocellular carcinoma patients with unresectable disease.

Continuing treatment of advanced hepatocellular carcinoma patients with unresectable disease.

Treatment should continue as long as the patient is clinically benefiting or until unacceptable toxicity occurs.

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

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third commonest cause of cancer death. In most instances, HCC is diagnosed only at intermediate to advanced stages and best supportive care is the most widely used option for patients with advanced HCC.

Sorafenib would be used in patients where curative treatment options have been exhausted, and where surgery or loco-regional therapy is not appropriate or has failed.

6. Comparator

The submission nominated placebo/best supportive care as the main comparators which may include antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management. The PBAC considered that this was appropriate.

7. Clinical Trials

The submission presented two randomised trials comparing sorafenib with placebo/best supportive care in patients with advanced hepatocellular carcinoma (HCC).

The trial published at the time of submission is as follows:

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
SHARP Trial Llovet et al.	Sorafenib improves survival in advanced Hepatocellular Carcinoma (HCC): Results of a Phase III randomized placebo-controlled trial (SHARP trial).	J Clin Oncology, ASCO Annual Meeting Proceedings Part I; 25 (18S). Abstract LBA1.

8. Results of Trials

The results for overall survival in the comparative trials are summarised below:

Analysis		Result (95% CI)	significance level needed*
SHARP Trial – Cutoff date = 17 October 2006 Pre-specified interim analysis Time-to-death – 321 events (Sorafenib: 143 deaths, Placebo: 178 deaths)			
Comparison of time-to-first event curves	1-sided stratified log rank test	P=0.000583	P=0.0073
		Median survival: sorafenib = 324 days (286, 405) placebo = 241 days (206, 276)	
	CPH	HR = 0.69 (0.55, 0.87)	NA
Supplementary Asia Pacific Trial - Cutoff date = 19 March 2007 Non-pre-specified interim analysis Time-to-death – 128 events (Sorafenib: 79 deaths, Placebo: 49 deaths)			
Comparison of time-to-first event curves	log rank test	P=0.040446	NS
		Median survival: sorafenib = 203 days (162, 235) placebo = 126 days (114, 166)	
	CPH	HR = 0.69 (0.48, 0.99)	NA

* Adjusted for alpha spending and any interim analyses
Abbreviations: NS=not specified, NA=not applicable, HR=hazard ratio, CPH=Cox proportional hazard model

The overall survival of sorafenib treated patients was superior to that of patients in the placebo arm, with a similar hazard ratio in the SHARP and Asia Pacific trials.

The result for time-to-symptom -progression (TTSP) from the comparative trials was not statistically significant.

The results for quality-of- life measures from the SHARP Trial were not statistically significant.

There were more serious adverse events, drug related adverse events, and Grade 3-4 hypertension, diarrhoea, oedema, and hand-foot skin reaction, and thrombocytopenia, and hypophosphatemia in sorafenib compared with BSC.

For PBAC's comments on these results, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed sorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care.

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

A modelled evaluation was presented with four health states – first line treatment/pre-progression, first line treatment/post-progression, BSC/post progression, and death using a ten year time horizon and one-monthly cycles. The model assumed continued sorafenib treatment beyond progression in 54.5% of patients for one month. Only treatment attributed adverse events of grade 3 or 4 severity occurring in at least 10% of sorafenib patients and considered to have cost consequences were included in the model.

Treatment effect and duration, model time horizon, extent of utility, and sorafenib price were the main drivers of the model.

The base case incremental cost effectiveness ratio (ICER) estimated in the economic model was in the range of $45,000- $75,000 per extra life year gained (LYG).

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5. The PBAC noted that there would be potential for use beyond progression in more patients and for longer duration.

12. Recommendation and Reasons

The PBAC recommended the listing of sorafenib on the PBS as an authority required benefit for advanced hepatocellular cancer (HCC) in patients who meet certain criteria on the basis of high but acceptable cost-effectiveness against best supportive care at the price proposed in the pre-PBAC response.

The PBAC agreed that the data from the Sharp trial suggest treatment with sorafenib is associated with a clinically meaningful improvement in survival in patients with advanced Barcelona Liver Clinic Cancer (BCLC) Stage C HCC, whose WHO performance status is 2 or less and who are Child Pugh class A. The Committee considered that the PBS listing restriction should incorporate these criteria for consistency with the Sharp trial.

Although the submission presented the results of the cost-effectiveness analysis only in terms of life-years gained, the Committee did not accept that it is appropriate to not quality adjust the incremental cost-effectiveness ratio (ICER) in this setting as this would imply an acceptance of the assumption that treatment for end of life conditions can be valued entirely upon the extent of survival benefit without consideration of any potential trade-off in terms of quality of the life. The Committee noted that although FACT-Hep (Functional Assessment of Cancer Therapy- Hepatobiliary) response rate at 12 weeks was significantly lower in the sorafenib arm of the SHARP trial compared with the placebo arm (P=0.04), there was no difference between study arms in FACT-Hep response rate at 12 weeks in the Asia-Pacific

trial (24.4% in the sorafenib arm and 26.9% in the placebo arm), despite almost identical overall survival outcomes in the trials.

The FACT-Hep consists of the 27-item FACT-G (General), which assesses generic health related quality of life (HRQL) concerns (in four domains, covering Physical, Social & family, Emotional, and Functional well-being), and the 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues (Heffernan et al. 2002). A mapping algorithm was developed by Dobrez et al. (2007), which found that the physical well being (PWB) and the functional well being (FWB) subscale correlated with utility values elicited using the time trade-off method. Although mapping could not be done due to the limited data from the SHARP study, the PWB and FWB subscales did not appear to be significantly different between the two treatment arms (p=0.084 and p= 0.806 respectively).

In regard to the effect of treatment on patient symptoms, the clinical status of subjects with HCC is often complicated by concomitant liver disease, deterioration of liver function and complications of underlying cirrhosis, clinical deterioration as a result of HCC progression, and/or the side effects of therapy. The Committee agreed that it is difficult to determine an appropriate utility value in this case because the disutility associated with the cancer per se cannot be reliably distinguished from any disutility due to liver disease, with any deterioration of liver function and complications of cirrhosis difficult to disentangle from the adverse effects of sorafenib.

However, the PBAC was of the view that the utility of a patient with advanced HCC would be less than 1, particularly as in the group of patients who are Child-Pugh-A (as specified by the restriction) liver function is not reduced at the beginning of treatment.

The Committee notes the extremely conservative respecification of the model suggested by the Economics Subcommittee (ESC) in which the treatment effect ceases after 2 years while the time horizon of the model was restricted to 5 years. However, the Committee considered, in light of recent evidence published in the European Journal of Cancer on the survival of patients with liver cancer (2008, 44: 1000 – 1006), that the approach adopted initially by the submission in which 10-year survival was modelled may not be unreasonable . Thus the Committee considered that the submission's base case incremental cost-effectiveness ratio of sorafenib over placebo in the range of $45,000 - $75,000 per life year gained was reasonable, which when quality adjusted would result in a ratio per quality-adjusted life-years gained more than $75,000. Although high, this incremental cost-effectiveness ratio was considered acceptable in light of the high clinical need given the absence of any other treatment option for the patients identified by the restriction, convincing clinical data from two well designed clinical trials, and small financial expenditure of less than $10 million in year 5.

Recommendation

SORAFENIB TOSYLATE, tablet, 200 mg (base)

Restriction	Authority Required Initial treatment, as the sole PBS subsidised agent, of advanced (BCLC Stage C) hepatocellular carcinoma in a patient with a WHO performance status of 2 or less and Child Pugh class A. Authority Required

	Continuing treatment, as the sole PBS subsidised agent, of advanced hepatocellular carcinoma in a patient who has previously been treated with PBS-subsidised sorafenib and who does not have progressive disease. NOTE: Sorafenib is not PBS-subsidised for adjunctive treatment after resection, ablation or chemoembolization. Sorafenib is not PBS-subsidised for maintenance therapy after disease progression. No applications for increased maximum quantities and/or repeats will be authorised
Maximum quantity:	120
Repeats:	2

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 chose not to comment.