PUBLIC SUMMARY DOCUMENT

Product: Sorafenib, tablet, 200 mg, Nexavar®
Sponsor: Bayer Australia Limited.
Date of PBAC Consideration: November 2013

1. Purpose of Application

The re-submission requested an Authority Required listing for the treatment, as the sole PBS-subsidised therapy, of Stage IV (advanced) clear cell variant renal carcinoma (RCC) in a patient who meets certain criteria.

2. Background

Sorafenib was previously considered for this indication at the November 2012 PBAC meeting. The submission was rejected on the basis that superior clinical effectiveness over best supportive care for the proposed PBS population had not been demonstrated.
The public summary document is available at the PBS website.

The PBAC had also previously rejected two submissions for sorafenib as first-line treatment for advanced RCC at the November 2006 and March 2008 meetings on the basis of high and uncertain cost-effectiveness ratios.

The PBAC noted that a submission for axitinib for the treatment of Stage IV clear cell renal carcinoma was also on its November 2013 meeting agenda and so considered the two medicines in relation to each other.

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, as the sole PBS subsidised therapy for the treatment of stage IV clear cell renal carcinoma in a patient who has failed therapy with PBS subsidised first line treatment and who meets the following criteria:

- Memorial Sloan Kettering Cancer Centre (MSKCC) score of favourable or intermediate risk group; AND
- WHO performance status of 2 or less

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

Note
RECIST Criteria are 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.

Listing was requested on the basis of a cost-effectiveness claim compared with best supportive care (BSC). The PBAC considered the proposed restriction's intention to restrict sorafenib to second-line treatment to be appropriate, given that sunitinib and pazopanib are listed on the PBS as first-line treatment for renal cell carcinoma, and that pivotal studies previously submitted did not support listing sorafenib in the first-line setting.

5. Clinical Place for the Proposed Therapy

Sorafenib is a multi-kinase inhibitor that targets various upstream receptor tyrosine kinases (c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-ß) and downstream RAF kinases (serine/threonine kinases) (CRAF, BRAF, V600E BRAF) in both the tumour cell and the tumour. While sunitinib and pazopanib target upstream receptor tyrosine kinases, sorafenib targets both upstream receptor tyrosine kinases and downstream serine/threonine kinase. The submission claimed that the difference accounts for the benefit of sorafenib being unaffected by prior failed treatment with a receptor tyrosine kinase inhibitor.

The submission proposed sorafenib as second-line therapy for stage IV clear cell renal cell carcinoma. There are currently no PBS-listed treatment options for the second-line treatment of stage IV clear cell renal cell carcinoma.

6. Comparator

The resubmission nominated best supportive care as the comparator. This was accepted as appropriate by the PBAC.

The PBAC considered that axitinib was also a relevant comparator.

7. Clinical Trials

One head-to-head trial comparing sorafenib and placebo was presented in the re-submission (Trial 11213; TARGET). This trial was also the basis for the November 2012 submission.

The PBAC recalled its concerns about the representativeness of Trial 11213 (patients received sorafenib after a cytokine) to the proposed PBS population (patients receive sorafenib after sunitinib or pazopanib). Therefore, this submission focused on evidence in patients previously treated with a tyrosine kinase inhibitor (TKI) or other regimens.

The re-submission presented an indirect comparison of sorafenib and BSC (using temsirolimus and everolimus as the common reference) based on two trials: INTORSECT and RECORD-1. The submission also presented a study comparing sorafenib with axitinib (AXIS).

INTORSECT is an open-label direct randomised trial in 512 patients with RCC who failed first-line sunitinib treatment. Patients were randomised to receive treatment with sorafenib 400mg twice daily or temsirolimus 25mg IV infusion once weekly. The treatment continued until disease progression, unacceptable toxicity or withdrawal.

The PBAC noted that this study was only provided as a conference presentation. This did not allow the PBAC to undertake a full and complete assessment of the information. In particular, the PBAC was concerned that the methods used for randomisation and concealment of allocation were unclear. The PBAC were therefore unable to assess the risk of bias in the design of the trial.

RECORD-1 is a double-blind randomised controlled trial of second-line or later-line treatment in 366 patients with RCC who may have failed multiple other regimens. Patients received either everolimus 10mg daily or placebo (BSC). The PBAC noted that more than 80% of patients in the BSC arm were permitted to cross over to everolimus after disease progression and therefore analysis of overall survival is likely to be significantly confounded.

AXIS is a randomised, open-label, multicentre trial in 723 patients with metastatic RCC following failure of one prior systemic first-line regimen. Patients were allocated to receive sorafenib 400mg twice daily or axitinib 2-10mg twice daily. The treatment continued until disease progression, unacceptable toxicity or withdrawal. The PBAC noted that this was an open label trial, but outcome assessors were blinded to treatment allocation and overall survival is an objective outcome.

The table below provides further information on the key studies presented in the re-submission.

Table B.5.2: Methods of analysis of the key outcomes used in the submission

Trial	Outcome	Method of statistical analysis
INTORSECT	Progression free survival	Stratified log-rank test for Cox proportional hazard with 95% CI, stratified for nephrectomy status, duration of response to sunitinib therapy, tumour histology, and MSKCC prognostic group.
	Overall survival	
RECORD-1	Progression free survival	Estimated with KM methods; treatment arms compared with stratified log-rank test adjusting for strata defined by MSKCC prognostic score and HR estimated by use of stratified Cox proportional hazards model. (Post-hoc exploratory analysis performed using RPSF time model to correct for crossover for overall survival)
	Overall survival	
AXIS	Progression free survival	Used KM methods with a stratified, one-sided, log-rank test adjusting for ECOG performance status and previous treatment was used to compared PFS between the two treatment groups. Cox proportional-hazards models used to explore potential effects of baseline stratification factors.
	Overall survival	Cox proportional hazard model, including treatment as a stratum, used to perform univariate analysis of OS. Variables significant at a 10% level in univariate analysis were used to construct the multivariate model for OS. A backward elimination process was applied, using a 5% significance level to stay in the model, to identify the final set of relevant factors.

8. Results of Trials

The submission reported the results for overall survival from INTORSECT, RECORD-1 and the indirect comparison. The PBAC agreed that overall survival was the most relevant outcome for decision making. However, the PBAC considered that the indirect comparison was not a valid basis for assessment of comparative effectiveness given the differences between the trial populations and the absence of any clinical evidence in the re-submission to support the claims that the common references (temsirolimus and everolimus) have equivalent safety and efficacy, and that everolimus is superior to BSC.

Instead, the PBAC considered the following summary of the intention to treat (ITT) results from the INTORSECT, RECORD-1 and AXIS trials as presented in the Economic Sub-Committee (ESC) Advice. The summary also includes the results of the TARGET trial, presented in the previous submission.

Comparison of OS and PFS results from key trials

	AXIS Sorafenib v axitinib N=723		**INTORSECT** Sorafenib v temsirolimus N=512		**RECORD-1** Everolimus v placebo N=366		**TARGET (Trial 11213)** Sorafenib v placebo N=769	
Patients	Sorafenib	Axitinib	Sorafenib	Temsirolimus	Everolimus	Placebo	Sorafenib	Placebo
	n=362	n=361	n=253	n=259	n=277	n=139	n=384	n=385
Overall survival, months	ITT=19.2 Sun=16.5	ITT=20.1 Sun=15.2	16.64	12.27	14.78	14.39	17.8	15.2
	$Difference_{ITT}$=-0.9 $Difference_{Sun}$=1.3		Difference=4.37		Difference=0.39		Difference = 2.6	
	HR_{ITT}=1.03 (0.85, 1.25) HR_{Sun}=1.003 (0.79, 1.78)		HR=**0.76 (0.61, 0.95)**		HR=0.87 (0.65, 1.17)		RR = 0.88 (0.74, 1.04)	
	Over approx. 3 years		Over approx. 4 years		Over approx. 2 years		Over approx. 2.8 years	
Died, n (%)	ITT=214 (60) Sun=131 (67)	ITT=211 (60) Sun=131 (68)	162 (64)	186 (72)	NR, K-M curve suggests about 60% in both arms		561/769 (73)	
Progression-free survival, months	ITT=4.7[a] Sun=3.4	ITT=6.7[a] Sun=4.8	3.91	4.28	ITT=4.9[b] Sun=3.9	ITT=1.9[b] Sun=1.8	5.5	2.8
	$Difference_{ITT}$=-2.0 $Difference_{Sun}$=-1.9		Difference=-0.37		$Difference_{ITT}$=3.0 $Difference_{Sun}$=2.1		Difference=2.7	
	HR_{ITT}=**1.50 (1.23, 1.84)**[a] HR_{Sun}=**1.35 (1.04, 1.75)**		HR=0.87 (0.71, 1.07)		HR_{ITT}=**0.33 (0.25, 0.43)**[b] HR_{Sun}=**0.34 (0.23, 0.51)**		HR=**0.44 (0.35, 0.55)**	
	Over approx. 3 years		Over approx. 4 years		Over approx. 2 years		Over approx. 1.1 years	

[a] Blinded Independent Committee Assessment
[b] Central radiology review

The PBAC noted that results from the INTORSECT trial indicate that overall survival was statistically significantly longer for sorafenib compared to temsirolimus [median OS (ITT) of 16.64 months versus 12.27 (HR=0.76, 95% CI: 0.61, 0.95)]. No significant differences in

overall survival were observed between everolimus and BSC in the RECORD-1 trial, with or without the results being adjusted for cross-over using the Inverse Probability of Censoring Weights (IPCW) and Rank Preserving Structural Failure Time (RPSFT) methods. No statistically significant difference in overall survival was observed between sorafenib and axitinib in the AXIS trial.

The PBAC noted that the primary outcome of progression free survival (PFS) in the INTORSECT trial was not statistically significant for sorafenib compared to temsirolimus, however the secondary outcome of overall survival was statistically significant with a p-value of 0.014. There was no explanation provided in the re-submission for the finding that overall survival improved in the sorafenib arm however PFS was unaltered. In these circumstances it is likely that factors other than exposure to the study drugs have influenced the survival outcome. These factors include cancer management delivered following disease progression. In this regard it would be important to present the data on management of all trial patients following disease progression.

Setting aside the discussion on overall survival, the PBAC recalled that oncology submissions have emphasised the patient relevance of changes in progression free survival and noted that this was quantitatively (albeit not statistically significantly) less in the sorafenib arm (3.91 months) compared with temsirolimus (4.28 months). For all these reasons, PBAC considered the results of this trial were not interpretable.

The PBAC noted that the re-submission presented no clinical evidence to support a claim of therapeutic equivalence between temsirolimus and everolimus as second-line therapies for RCC, or any other indication. The re-submission argued that despite some differences (e.g., metabolism, formulation, dosing and route), temsirolimus and everolimus are closely related in terms of chemical structure, pharmacology, therapeutic activity and adverse events. The PBAC noted that median overall survival in the temsirolimus arm of INTORSECT was 12.27 months compared with 14.78 months in the everolimus arm of RECORD-1, and considered the difference may be attributable to (i) the differences between the therapies themselves; or (ii) the differences in trial populations.

The PBAC noted that overall survival was not statistically significantly different between everolimus and BSC in RECORD-1. However this result was likely biased towards BSC due to extensive cross-over. The PBAC has previously "considered that there was uncertainty about a conclusion of superior efficacy in mRCC with everolimus compared with placebo [for BSC] based on the benefit in terms of progression free survival, when no benefit in terms of overall survival or quality of life was observed in RECORD-1" (Everolimus PSD July 2010).

Similarly, the PBAC has previously stated that "that there was uncertainty about the magnitude of the treatment effect of temsirolimus compared with BSC" in advanced RCC (Temsirolimus PSD July 2008).

With regard to comparative harms, although new safety data were presented in this re-submission, the PBAC noted that the toxicity profile of sorafenib remained unchanged from the previous submission (based on Trial 11213 (TARGET), comparing sorafenib with placebo).

In comparison with axitinib, hand-foot skin syndrome (51% v 27%; RR=1.87; 95% CI: 1.53, 2.27), rash (32% v 13%; RR=2.52; 95% CI: 1.84, 3.44) and alopecia (32% v 4%, RR=8.31; 95% CI: 4.86, 14.18) were reported more frequently with sorafenib; whereas hypertension (29% v 40%; RR=0.72; 95% CI:0.58, 0.88), nausea (22% v 32%, RR=0.67; 95% CI: 0.52, 0.86), dysphonia (14% v 31%; RR=0.44, 95% CI: 0.32, 0.59) and hypothyroidism (8% v 19%, RR=0.43; 95% CI: 0.28, 0.64) were reported less frequently.

No new safety concerns were identified in the extended assessment of comparative harms.

9. Clinical Claim

The submission described sorafenib as superior in terms of effectiveness and inferior in terms of safety compared to BSC (placebo).

The PBAC considered that the results of the indirect comparison did not provide a reliable basis for estimating the effectiveness of sorafenib over BSC.

The PBAC considered that the available data, including the head-to-head AXIS trial, appeared to demonstrate non-inferior efficacy between sorafenib and axitinib.
The PBAC noted the sponsor's comments in its pre-PBAC response that the recommended doses in the AXIS trial were 5 mg twice daily for axitinib and 400 mg twice daily for sorafenib given daily until disease progression. The actual dose intensity (actual total dose / intended dose) was 99% for axitinib and 92% for sorafenib, meaning that the equi-effective doses are close to 5 mg twice daily and 400 mg twice daily.

10. Economic Analysis

The submission presented a modelled economic evaluation (cost utility analysis, CUA) based on the claim of superior efficacy. The re-submission presented an ICER in the range of $15,000-$45,000/ quality adjusted life year (QALY) based on the overall survival outcome from the trials (as generated by the indirect comparison), applied to an advanced RCC population undergoing second-line treatment.

The time horizon of the model was three years, thus data from INTORSECT did not require extrapolation (trial duration of 4 years), whereas data for RECORD-1 were extrapolated to 3 years (from a trial duration of 20 months). An average utility weight (0.72) was applied to patients who are alive in the model, this represented the mid-point between patients with progressed (0.68) and non-progressed (0.76) advanced RCC disease, sourced from the sunitinib submission to NICE (based on Motzer et al, 2006). Motzer (2006) was presented in the November 2012 re-submission, and 0.72 was the same utility value applied to patients treated with BSC in the March 2008 re-submission.

The PBAC considered that the submission's approach was consistent with its clinical claim, but was not adequately supported by the evidence presented. As the clinical efficacy was not substantiated the PBAC did not find the economic modelling to be valid or informative.

11. Estimated PBS Usage and Financial Implications

The submission used an epidemiological approach, supplemented with utilisation data, to estimate the utilisation and financial implications associated with the requested PBS listing of sorafenib.

The likely number of patients eligible for treatment with sorafenib per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

The PBAC noted the Drug Utilisation Sub-Committee (DUSC) advice that it considered the re-submission had underestimated use of sorafenib in Year 1, but the estimates in the remaining years may be reasonable overall, when sorafenib is used within the proposed restriction.

12. Recommendation and Reasons

The PBAC rejected the submission to list sorafenib on the PBS for the second line treatment of stage IV renal cell carcinoma on the basis of inadequate evidence of proven superior efficacy over BSC.

The PBAC considered the critical issue in the submission was the indirect comparison. The PBAC considered that the indirect comparison was not a valid basis for assessment of comparative effectiveness given the differences between the trial and the absence of any evidence in the re-submission to support the claims that the common references (temsirolimus and everolimus) have equivalent safety and efficacy, and that everolimus is superior to BSC.

Because the claim of clinical efficacy was not substantiated by the data presented, the PBAC did not find the economic modelling to be valid or informative.

The PBAC considered that the results of the AXIS trial would support a conclusion of non-inferiority of axitinib to sorafenib.

The PBAC considered that the INTORSECT trial had not demonstrated that the statistically significant difference in overall survival was attributable to treatment with sorafenib. It was considered that overall survival gains should line-up with progression free survival changes and that post progression treatment or adverse side effects may well have influenced the overall survival results of the INTORSECT trial. No data was provided in the submission to explain why progression free survival in sorafenib was quantitatively less than temsirolimus yet overall survival was greater. For these reasons, PBAC considered the results of this trial uninterpretable for reimbursement decision making.

The PBAC noted that data from the INTORSECT trial were only provided in the submission in a conference presentation format. The PBAC considered that this was inappropriate and did not allow adequate assessment of the trial's quality and validity.

The PBAC acknowledged that a clinical need exists for treatment of Stage IV RCC, noting that no second line treatments are currently available on the PBS. The PBAC also acknowledged the views of consumers, healthcare professionals and organisations, received via the Consumer Comments facility on the PBS website regarding the unmet clinical need for PBS subsidised therapies for the second-line treatment of stage IV renal cell carcinoma and in support of the submission. However, the PBAC considered that recommending treatment options on the PBS for renal cell carcinoma in the second line setting would still need to be made based on strong clinical evidence supporting clinical efficacy over BSC.

The PBAC noted that the submission meets the criteria for an Independent Review.

Outcome:
Rejected

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 had no comment.