

PUBLIC SUMMARY DOCUMENT

Product: Sorafenib, tablet, 200 mg (as tosylate), Nexavar[®]

Sponsor: Bayer Australia Limited

Date of PBAC Consideration: November 2012

1. Purpose of Application

The resubmission sought an extension to the current Authority Required listing to include the initial and continuing treatment of Stage IV clear cell renal carcinoma in a patient who has failed therapy with first line treatment and who meets certain criteria.

2. Background

Sorafenib is currently PBS-listed for the treatment of advanced (BCLC Stage C) hepatocellular carcinoma.

There have been two previous submissions for sorafenib for the indication of renal cell carcinoma. The original submission in November 2006 and a re-submission in March 2008 requested an Authority Required listing for the initial and continuing treatment of advanced (unresectable or metastatic) renal cell carcinoma. Both submissions positioned sorafenib as first-line treatment. The current resubmission positioned sorafenib as second-line treatment.

See the November 2006 and March 2008 sorafenib Public Summary Documents for further information.

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 first line treatment option:

AND

Who meet 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 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

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Currently, sunitinib and pazopanib are two drugs currently listed on the PBS as first-line therapy for the treatment of stage IV clear cell variant renal cell carcinoma.

The submission proposed sorafenib as a second-line treatment option for patients with stage IV clear cell renal carcinoma who have failed first-line therapy.

6. Comparator

The re-submission nominated placebo/best supportive care (BSC) as the main comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The re-submission was based on one randomised controlled trial comparing sorafenib with placebo in 903 patients with stage IV RCC, Trial 11213. This was the same trial presented in the November 2006 submission and the March 2008 re-submission. The current re-submission presented a new analysis of overall survival of Trial 11213 using rank preserving structural failure time (RPSFT) analysis, which is used to correct for the effect of patient cross-over in the trial.

For PBAC's view, see Recommendations and Reasons.

The table below details the published trials presented in the submission.

Trial ID/First author	Protocol title/Publication title	Publication citation
Trial 11213		
Escudier B et al.	Sorafenib in advanced clear-cell renal-cell carcinoma.	<i>New England Journal of Medicine</i> (2007); 356(2): 125-134
Escudier B et al.	Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial.	<i>Journal of clinical oncology: official journal of the American Society of Clinical Oncology</i> (2009); 27(20): 3312-3318.
Bukowski R et al.	Effects of sorafenib on symptoms and quality of life: Results from a large randomized placebo-controlled study in renal cancer.	<i>American Journal of Clinical Oncology: Cancer Clinical Trials</i> (2007); 30(3): 220-227.
Lamuraglia M et al.	To predict progression-free survival and overall survival in metastatic renal cancer treated with sorafenib: Pilot study using dynamic contrast-enhanced Doppler ultrasound.	<i>European Journal of Cancer</i> (2006); 42(15): 2472-2479.

Antoun S et al.	Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: Results from a placebo-controlled study.	<i>Journal of Clinical Oncology</i> (2010); 28(6): 1054-1060.
Bellmunt J et al.	Sorafenib TARGET trial results in Spanish patients.	<i>Clinical and Translational Oncology</i> (2007); 9(10): 671-673.
Bukowski R et al.	Efficacy and safety of sorafenib in patients with advanced clear-cell renal-cell carcinoma (RCC) with bone metastases: Results from the phase III target study.	<i>European Journal of Cancer</i> (2009); Supplement 7(2-3): 432.
Eisen T et al.	Sorafenib for older patients with renal cell carcinoma: Subset analysis from a randomized trial.	<i>Journal of the National Cancer Institute</i> (2008); 100(20): 1454-1463
Gschwend JE et al.	Efficacy and safety of sorafenib in patients with advanced clear-cell renal-cell carcinoma (RCC) with bone metastases: Results from the phase III TARGET study.	<i>Onkologie</i> (2010); 33(6): 130-131.
Hahn OM et al.	Dynamic contrast-enhanced magnetic resonance imaging pharmacodynamic biomarker study of sorafenib in metastatic renal carcinoma.	<i>Journal of Clinical Oncology</i> (2008); 26(28): 4572-4578.
Hutson TE et al.	Long-term safety of sorafenib (SOR) for the treatment (tx) of advanced clear-cell renal-cell carcinoma (RCC): Data analysis from patients (pts) treated for over 1 year in the phase III TARGET study.	<i>Journal of Clinical Oncology</i> (2009); 27(15): e16057.
Massard C et al.	Incidence of brain metastases in renal cell carcinoma treated with sorafenib.	<i>Annals of Oncology</i> (2010); 21(5): 1027-1031.
Negrier S et al.	Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET.	<i>Medical Oncology</i> (2010); 27(3): 899-906.
Oudard S et al.	Efficacy and safety of sorafenib in patients with advanced clear-cell renal cell carcinoma (RCC) with diabetes: Results from the phase III TARGET study.	<i>Journal of Clinical Oncology</i> (2009); 27(15): e16099.
Pena C et al.	Biomarkers predicting outcome in patients with advanced renal cell carcinoma: Results from sorafenib phase III treatment approaches in renal cancer global evaluation trial.	<i>Clinical Cancer Research</i> (2010); 16(19): 4853-4863.
Pena C et al.	Plasma biomarkers predicting outcome in patients with advanced RCC: Results from the sorafenib phase III TARGET trial.	<i>Molecular Cancer Therapeutics</i> (2009); 8(12).
Trump DL commentary of Escudier B et al. TARGET Study	Sorafenib in advanced clear-cell renal-cell carcinoma.	<i>Urologic Oncology: Seminars and Original Investigations</i> (2007); 25(5): 443-445.

Group		
NA-ARCCS		
Stadler WM et al.	Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America.	<i>Cancer</i> (2010); 116(5): 1272-1280.

8. Results of Trials

. The re-submission only presented relative difference; absolute difference in median death time was calculated during the evaluation and was in the range of 2.9 months to 3.1 months in the RPSFT analysis (depending on weighting) favouring sorafenib. The intention-to-treat (ITT) and placebo censored analyses were presented in previous submissions. All RPSFT analysis methods produced statistically significant hazard ratios (HRs) at the alpha=0.05 level between 0.81 (weighted) and 0.83 (unweighted). All of the estimated values of ψ_0 (the acceleration factor) were negative, indicating that sorafenib extends the lifetime of patients relative to placebo. The results of the post-hoc exploratory RPSFT analysis of Trial 11213 provided an adjusted estimate of the difference in overall survival between sorafenib and placebo, and were useful as a ‘compromise’ estimate between the estimates provided by the interim ITT analysis and the final (null-biased) ITT analysis. While the RPSFT analysis presented in the re-submission indicated statistically significant survival gains for sorafenib, the re-submission did not apply these results to the modelled evaluation.

For PBAC’s view, see Recommendations and Reasons.

The toxicity profile of sorafenib remained unchanged from that presented in the March 2008 re-submission. Sorafenib is associated with a number of adverse events compared to placebo including diarrhoea, rash/desquamation, hand-foot skin reaction, alopecia, as well as hypertension, pruritus, and dermatology (other). The re-submission also presents a summary of data from the 2011 Periodic Safety Update Report for sorafenib and data obtained from a literature search for relevant longer-term safety data. The re-submission concluded that the additional data is in accordance with the established overall safety profile of sorafenib.

9. Clinical Claim

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

The PBAC did not accept the submission’s clinical claim in the context of the proposed listing. *See Recommendation and Reasons.*

10. Economic Analysis

The re-submission presented a cost-utility analysis based on the claim of superior efficacy of sorafenib compared to placebo/BSC. The model calculated an ICER in the range of \$45,000 - \$75,000/QALY based on overall survival from Trial 11213 and extrapolated to 5 years (from 1.5 years in the trial). Utility weights were literature-based, with the utility difference between sorafenib and placebo being the midpoint of calculated utility values for progressed and non-progressed patients.

For PBAC’s view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of 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.

12. Recommendation and Reasons

The PBAC considered the proposed restriction's intent 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.

The re-submission's nominated main comparator of placebo/best supportive care (BSC) was considered appropriate by the PBAC.

The representativeness of the Trial 11213 population (patients received sorafenib after a cytokine) to the proposed PBS population (patients receive sorafenib after sunitinib or pazopanib) was of significant concern to the PBAC. The PBAC further noted that the submission attempted to address the question of whether the type of first-line therapy is a treatment effect modifier for second-line therapy. Overall, the evidence presented by the re-submission did not allow the PBAC to rule out that the type of first-line treatment received is a treatment effect modifier for second-line treatment. Therefore, the PBAC did not accept the applicability of the trial results to the proposed PBS population.

The PBAC considered the evidence from observational and randomised controlled trials of sorafenib used in the second-line setting in tyrosine-kinase inhibitors exposed patients to be either weak, supportive of the case that sorafenib is inferior to other agents or demonstrates that there is a difference in response between post-cytokine and post sunitinib patients in terms of PFS. The submission's clinical claim that sorafenib is superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo was reasonable in the context of a patient population receiving cytokine therapy as first-line therapy but because sunitinib and pazopanib are now available on the PBS as first-line therapy, the PBAC did not accept the submission's clinical claim in the context of the proposed listing.

The re-submission presented a cost-utility analysis based on the claim of superior efficacy of sorafenib compared to placebo/BSC. The PBAC noted that the model calculated an ICER in the range of \$45,000 - \$75,000/QALY based on overall survival from Trial 11213 and extrapolated to 5 years (from 1.5 years in the trial). The PBAC noted that there was a high level of uncertainty in the base case ICER, with sensitivity analyses indicating that the model is most sensitive to changes in treatment effect and duration of benefit (the ICER increased to greater than \$200,000/QALY using upper 95% CI of treatment effect and to an ICER in the range of \$75,000 - \$105,000/QALY with duration of benefit ceased at one year). However, because the PBAC was not convinced that sorafenib is superior to placebo/BSC since the evidence base was in patients who had predominantly had cytokine as first-line therapy, the PBAC did not find the economic modelling to be informative.

The PBAC therefore rejected the submission on the basis that superior clinical effectiveness of sorafenib over BSC for the proposed PBS population had not been demonstrated. The

PBAC noted that data to inform the comparison of sorafenib and placebo in patients who have failed first line tyrosine kinase inhibitors (sunitinib/pazopanib) was very limited. The PBAC considered these data to be crucial to the economic model and that the extent of uncertainty in the effectiveness data had substantial implications for interpreting the modelled incremental cost effectiveness ratio.

The PBAC acknowledged and noted the consumer comments on this item. The PBAC further acknowledged Kidney Health Australia's letter of support for the need to have second line treatments available for renal cell carcinoma on the PBS. However, the PBAC considered that recommending further treatment options on the PBS for renal cell carcinoma in the second line setting would still need to be made on the basis of strong clinical evidence in the Australian clinical treatment context.

Recommendation:

Reject

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 Limited is disappointed by this decision, however looks forward to working collaboratively with the PBAC to make sorafenib available to Australian patients with renal cell carcinoma.