

PUBLIC SUMMARY DOCUMENT

Product: PAZOPANIB, tablets, 200 mg and 400 mg (as hydrochloride), Votrient[®]

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought an Authority required listing for the treatment of stage IV advanced and/or metastatic, clear cell variant, renal cell carcinoma (RCC) in an adult patient who meets certain criteria.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Pazopanib 200 mg and 400 mg capsules were TGA registered on 20 June 2010 for the treatment of advanced and/or metastatic renal cell carcinoma (RCC).

4. Listing Requested and PBAC's View

The sponsor proposed a revised listing in the Pre-Sub Committee Response as follows:

Authority required

Initial therapy

Initial treatment, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who meets the Memorial Sloan Kettering Cancer Centre (MSKCC) low to intermediate risk group and have a WHO performance status of 2 or less and who has not previously been issued with a PBS authority prescription for sunitinib malate.

NOTE:

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

Continuation

Continuing treatment beyond 3 months, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who has previously been issued with an authority prescription for pazopanib 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 Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Renal cell carcinoma (RCC) is a form of kidney cancer that arises from the cells of the renal tubule. Advanced RCC is often refractory to treatment and associated with a poor prognosis.

Currently, only sunitinib is PBS listed for this indication. Pazopanib is proposed as an alternative treatment option for the first-line treatment of advanced RCC.

6. Comparator

The submission nominated sunitinib as the main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented three randomised trials to conduct a two-step indirect comparison of pazopanib and sunitinib. Trial VEG105192 compared pazopanib 800 mg/day with placebo, trial A6181034 compared sunitinib 50 mg/day (4 weeks active treatment followed by 2 week break) with interferon-alfa 2a and trial MRC compared interferon-alfa 2b with methoxyprogesterone acetate (MPA) in patients with stage IV renal cell carcinoma (RCC). Since no common comparator was identified for pazopanib and sunitinib, the submission assumed MPA to be equivalent to placebo.

Details of the published trials included in the submission are presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Pazopanib vs placebo		
VEG105192 Sternberg et al (2010)	Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomised Phase III Trial.	J Clin Oncol 28(6): 1061-1068
INF-α vs sunitinib		
A6181034 Mozter et al (2007)	Sunitinib versus Interferon Alfa in Metastatic Renal Cell Carcinoma	NEJM 356(2): 115-124
Cella et al (2008)	Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomised trial.	J Clin Oncol 26(22): 3763-3769
Mozter et al (2009)	Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma.	J Clin Oncol 27(22): 3584-3590
Fayers et al (1994)	On the development of the medical research council trial of interferon in metastatic renal carcinoma. EMA Scientific Discussion of Trial A6181043.	Statistics in Medicine 13: 2249-2260. Available from: www.emea.europa.eu/humandocs/humans/epar/sutent.htm
MPA (assumed equivalent to placebo) vs IFN-α		
MRC Ritchie et al (1999)	Interferon-alfa and survival in metastatic renal cell carcinoma: early results of a randomised controlled trial.	Lancet 353(9146): 14-17.

8. Results of Trials

The submission nominated progression-free survival (PFS) as the primary endpoint for the indirect comparisons. PFS was the primary endpoint in trials VEG105192 and A618034 and was a key secondary endpoint in trial MRC.

Progression-free survival results for the pazopanib trial are presented in the table below.

Results of progression-free survival (PFS) in Trial VEG105192 of pazopanib versus placebo

Analysis of PFS	No. events (death or progression)		HR (95% CI) P value	Median time to progression (Months) (95%CI)	
	Pazopanib	Placebo	Pazopanib vs placebo	Pazopanib	Placebo
ITT	148/290	98/145	0.46 (0.34, 0.54) p<0.0000001	9.2 (7.4, 12.9)	4.2 (2.8, 4.2)
cytokine naïve	73/155	57/78	0.40 (0.27, 0.60) p <0.0000001	11.1 (7.4,14.8)	2.8 (1.9, 5.6)
cytokine pretreated	75/135	41/67	0.54 (0.35, 0.84) p= 0.0002560	7.4 (5.6,12.9)	4.2 (2.8, 5.6)

Statistically significantly increased PFS was observed in patients treated with pazopanib compared with placebo, for the ITT population and cytokine naïve and pre-treated populations.

The PBAC noted that the indirect comparison of PFS in cytokine naïve patients illustrated that pazopanib treatment is associated with a higher hazard of disease progression compared with sunitinib, however this difference was not statistically significant.

The PBAC also noted that results of additional sensitivity analyses using PFS HR results of ITT and cytokine pre-treated populations of Trial VEG105192 showed that pazopanib is consistently associated with a higher hazard compared to sunitinib. Furthermore, when results of the cytokine pre-treated patients was used, pazopanib treatment was associated with a statistically higher risk of disease progression.

The PBAC noted that the pazopanib, sunitinib and comparator trials differed in disease severity, the proportion who had a nephrectomy and the proportion who had previous cytokine treatment. The trials were also conducted over a 15 year time span, where standard treatments are likely to have changed. The PBAC considered it was therefore uncertain whether the trial populations were sufficiently comparable to provide a meaningful indirect comparison, given the observed differences in the baseline characteristics of patients in these trials.

The PBAC noted that final overall survival results were not yet available for the pazopanib trial, limiting the usefulness of an indirect comparison based on overall survival.

The incidence of adverse events (AEs) reported during the pazopanib trial was higher in the pazopanib arm (92%) compared with placebo (74%) mostly related to grade 1 and 2 AEs, whereas the overall incidence of AEs reported in the sunitinib trial was not statistically significantly different across arms (99% vs 98%), albeit with an active comparator. In Trial VEG105192 44/290 (15%) of the patients in the pazopanib arm and 8/78 (6%) of the patients

in the placebo arm reported AEs leading to discontinuation. Liver function/enzyme abnormalities (including ALT, AST, hepatotoxicity, hepatic enzyme and hyperbilirubinemia) led to discontinuation of pazopanib for 11/290 (3.8%) patients in the pazopanib arm. Trial A6181034 reported that a total of 23/375 (6%) of sunitinib patients discontinued due to an adverse event compared with 34/360 (9%) patients in the IFN treatment arm.

Trial VEG105192 reported 109/290 (38%) deaths in the pazopanib arm and 67/145 (46%) in the placebo arm.

The submission highlighted that sunitinib had a higher incidence of the following grade 3 and grade 4 adverse events compared to pazopanib: asthenia, dyspnoea, fatigue, hand-foot syndrome, hypertension, nausea and neutropenia. The grade 3 and 4 adverse events which appeared to occur more frequently with pazopanib compared to sunitinib are liver tests ALT and AST.

For PBAC's views on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described pazopanib as non-inferior in terms of comparative effectiveness and having a more favourable safety profile over sunitinib.

For PBAC's view, see Recommendation and Reasons.

The PBAC noted that a non-inferiority, head-to-head trial of pazopanib versus sunitinib is currently underway and the comparative effectiveness and safety of pazopanib and sunitinib would be easier to discern from the results of that trial.

10. Economic Analysis

The submission presented a cost minimisation analysis. The submission used an average monthly treatment cost approach given the differences in dosage regimens (i.e. pazopanib is administered continuously daily whereas sunitinib is administered daily for 4 consecutive weeks followed by 2 weeks off).

11. Estimated PBS Usage and Financial Implications

The submission estimated financial savings per year to the PBS of less than \$10 million in Year 5, mainly due to increases in patient co-payments for pazopanib due to more frequent dispensing (4 weekly vs 6 weekly). The submission's estimate was considered uncertain due to uncertain assumptions of market growth, the proportion of sunitinib 12.5 mg dispensed to be used as part of the 37.5 mg/active day dose and market uptake of pazopanib.

12. Recommendation and Reasons

The PBAC noted that the clinical treatment algorithm and associated restriction wording for pazopanib had changed quite significantly during the evaluation process. Initially the submission sought PBS-listing for pazopanib as an alternative to sunitinib in tyrosine kinase inhibitor (TKI) treatment naïve patients, and in patients receiving sunitinib who wished to switch to pazopanib for reasons other than disease progression (eg intolerance to sunitinib). During the evaluation, the sponsor narrowed the restriction to limit treatment with pazopanib and by extension, sunitinib, to TKI naïve patients, thus positioning pazopanib as a direct substitute for sunitinib only in TKI naïve patients only. The PBAC considered this to be

clinically inappropriate as the highest area of current clinical need is for patients who are so intolerant to sunitinib and consequently need to cease therapy. Also, it is highly likely that in practice, pazopanib will be used in patients whose disease has progressed while on treatment sunitinib, and vice versa, and any listing proposal for pazopanib needs to adequately deal with this scenario.

The PBAC agreed that sunitinib is the most appropriate comparator for pazopanib in TKI treatment naïve patients, but that best supportive care is also an appropriate comparator in sunitinib intolerant patients and patients whose disease has progressed on sunitinib.

The PBAC noted that the submission presented a two step-indirect comparison, to compare pazopanib and sunitinib, using interferon- α and placebo/ medroxyprogesterone acetate (MPA) as the common comparators. The PBAC agreed that this comparison has a number of problems as documented by the ESC. Furthermore, the submission's indirect comparison of progression free survival (PFS) in cytokine naïve patients, considered appropriate by PBAC as the comparison most representative of the Australian patient population, demonstrates that pazopanib treatment is associated with a higher hazard of disease progression compared with sunitinib. The PBAC agreed with its ESC that although the PFS for pazopanib treated patients is not statistically significantly different from the PFS for sunitinib treated patients, the point estimate suggests pazopanib is worse than sunitinib. Thus, PBAC concluded that the submission's claim of non-inferiority is not supported.

With respect to the comparison of the safety of pazopanib and sunitinib, the PBAC noted that although the two drugs have different toxicity profiles, it is less clear that pazopanib has a more favourable safety profile than sunitinib as claimed by the submission.

The Committee noted that a head-to-head, non-inferiority trial of pazopanib versus sunitinib is currently underway, with results due to be available in 2011. The PBAC considered that the results from this trial are necessary to address the current uncertainty around the comparative efficacy and safety of pazopanib and sunitinib.

The PBAC therefore rejected the submission because the proposed PBS-restriction is clinically inappropriate and does not reflect the treatment algorithm which would result if pazopanib were to be PBS-listed. Additionally, based on the currently available data, there is significant uncertainty as to whether pazopanib is non-inferior to sunitinib in the treatment of stage IV advanced and/or metastatic, clear cell variant, renal cell carcinoma.

The PBAC noted the Pre-PBAC Response proposal for a Managed Entry Scheme, but considered that this would only be appropriate in the context of a lower price for pazopanib than sunitinib. Further, it would be inappropriate to expose patients to a potentially inferior drug until evidence has been produced to show the contrary.

The PBAC noted that the submission meets the criteria for an independent review.

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

GlaxoSmithKline is disappointed by the decision but will continue to work with the PBAC to make the product available for the suggested patient population and will provide a new application as soon as additional data is available.