PUBLIC SUMMARY DOCUMENT
Product: PAZOPANIB, tablet, 200 mg and 400 mg (as hydrochloride), Votrient®
Sponsor: GlaxoSmithKline Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The resubmission sought an Authority Required listing for the initial and continuing treatment as the sole PBS subsidised tyrosine kinase inhibitor (TKI) therapy of stage IV clear cell variant renal cell carcinoma (RCC) in a newly diagnosed patient who meets certain criteria.

2. Background

This was the second consideration by the PBAC of an application to list pazopanib for treatment of RCC.

At its July 2010 meeting, the PBAC rejected an application for listing of pazopanib because the proposed PBS-restriction was clinically inappropriate and did not reflect the treatment algorithm that would result if pazopanib were to be PBS-listed. Additionally, based on the data available at the time, there was significant uncertainty as to whether pazopanib was non-inferior to sunitinib in the treatment of stage IV advanced and/or metastatic, clear cell variant RCC.

A copy of the Public Summary Document (PSD) from the July 2010 meeting is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Pazopanib-july10.

3. Registration Status

Pazopanib was TGA registered on 30 June 2010 for the treatment of advanced and/or metastatic renal cell carcinoma (RCC).

4. Listing Requested and PBAC's View

Authority Required
Initial treatment, as the sole PBS-subsidised tyrosine kinase inhibitor (TKI) 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, has a WHO performance status of 2 or less and has not previously received PBS-subsidised TKI therapy for this condition.

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

Authority Required
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.

Authority Required
Initial treatment, as the sole PBS-subsidised therapy, of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who was receiving treatment with pazopanib prior to [effective listing date].

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

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.

The resubmission proposed that the place in therapy of pazopanib is as an alternative first-line treatment to sunitinib for patients with advanced or metastatic RCC.

6. Comparator

The resubmission nominated sunitinib as the main comparator. The PBAC has previously agreed that this was the most appropriate comparator in TKI treatment naïve patients.

7. Clinical Trials

The resubmission presented the same trials considered previously by the PBAC, with updated results for Trial VEG105192:

- Trial VEG105192: direct comparison of pazopanib 800 mg/day and placebo;
- Trial MRC-RE01: direct comparison of medroxyprogesterone acetate (MPA; 300 mg/day) versus interferon-α-2b (10MU three times a week); and
- Trial A6181034: direct comparison of sunitinib (50 mg/day over 4 weeks with 2 weeks of no treatment (a 6-week cycle)) versus interferon-α-2a (9MU three times a week) in patients with RCC.

Details of the published trials have been previously reported in the July 2010 PSD.

8. Results of Trials

The key results are summarised in the table below. Results for the primary outcome of progression-free survival (PFS) in the previous submission (July 2010) were those reported for "Independent Review".

Results of the primary outcome of progression-free survival (PFS) in Trial VEG105192, ITT and treatment naïve

Analysis of PFS	n/N (%) (death or progression)		HR (95% CI) P value	Median time to progression in months (95%CI)	
	Pazopanib	Placebo		Pazopanib	Placebo
Population (ITT)					
Independent Review	148/290 (51)	98/145 (68)	**0.46 (0.34, 0.54)** p<0.0000001	9.2 (7.4, 12.9)	4.2 (2.8, 5.6)
Population (treatment-naïve)					
Independent Review	73/155 (47)	57/78 (73)	**0.40 (0.27, 0.60)** p<0.0000001	11.1 (7.4, 14.8)	2.8 (1.9, 5.6)

Bold typography indicates statistically significant differences

Sensitivity analyses were also conducted whereby PFS was analysed using investigator assessment of progression (as opposed to the independent review committee approach), and using actual scan dates to determine dates of censoring and progression. The re-submission used the results reported for "Based on Scan Date" in its base case indirect comparison.

A statistically significant difference in progression-free survival, favouring pazopanib, was demonstrated for each basis of analysis in the treatment-naïve population and in the intention to treat (ITT) population.

No statistically significant differences in terms of overall survival (OS) were observed between pazopanib and placebo (for the ITT or treatment-naïve populations), however these results were confounded given that patients randomised to placebo could initiate treatment with pazopanib upon disease progression in the trial. The various methods used to adjust for the confounding of patients crossing over in the VEG105192 trial [inverse probability of censoring weights (IPCW) and rank preserving structural failure time (RPSFT)] increased the point estimates of the benefits of pazopanib compared with placebo considerably, however the methods did not result in demonstrating a statistically significantly difference between treatments.

A statistically significant difference in both PFS and OS was observed in the A6181034 and MRC-RE01 trials, favouring sunitinib and interferon-α, respectively, regardless of the type of analysis.

The results of the base case indirect comparison for pazopanib and sunitinib for PFS and OS demonstrated that there was no significant difference between pazopanib and sunitinib for PFS. Similarly, the results of the base case indirect comparison demonstrated that there is no significant difference between pazopanib and sunitinib for OS.

For PBAC's view of these results, see Recommendation and Reasons.

The resubmission presented new toxicity data from the updated trial report. The PBAC noted that these were not materially different to those presented in the previous submission.

9. Clinical Claim

The resubmission claimed that pazopanib had likely similar efficacy and safety outcomes compared to sunitinib, but noted that there was insufficient clinical evidence to demonstrate a clear non-inferiority to sunitinib.

The PBAC concluded that, on the basis of the evidence available, pazopanib was non-inferior to sunitinib in terms of effectiveness and had a different side-effect profile.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The resubmission presented a cost minimisation analysis. A relativity factor of 1 mg sunitinib equals 24mg pazopanib was applied across the entire dosing range.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The resubmission estimated the likely number of packs dispensed per year to be less than 10,000 in Year 5, with estimated net savings to the PBS.

12. Recommendation and Reasons

The PBAC recommended listing pazopanib on the PBS as the sole PBS-subsidised therapy for certain patients with renal cell carcinoma on a cost-minimisation basis compared with sunitinib, whilst also noting that some considerations previously relevant to sunitinib do not apply to pazopanib. The PBAC advised that the relevant dose relativity in this context is 1 mg sunitinib to 24 mg pazopanib.

The PBAC recommended that the PBS restriction exclude the possibility of sequential use of sunitinib and pazopanib being subsidised by the PBS except in the circumstance of failure due to intolerance.

The PBAC concluded that, on the basis of the evidence available, pazopanib is non-inferior to sunitinib in terms of effectiveness and has a different side-effect profile. Patients taking sunitinib tend to experience events such as diarrhoea, fatigue, hypertension, mucositis, hand-foot syndrome, and myelosuppression; patients taking pazopanib tend to experience diarrhoea, hypertension and liver dysfunction. These differences are insufficient to change an overall conclusion that pazopanib is non-inferior to sunitinib in terms of safety.

The PBAC considered that there was a weak evidentiary basis for determining clinical non-inferiority contained in the submission and this evidence could not support a conclusion of superiority of one drug over the other. In this regard, PBAC also noted that randomised trials directly comparing the two drugs in relevant populations were underway that were capable of addressing this issue with greater scientific rigour.

Similarly, the PBAC considered that there was also a weak evidentiary basis for determining the equi-effective doses in the submission to support the proposed cost-minimisation approach. However, the PBAC reviewed PBS utilisation data, which were consistent with the dose and the duration of sunitinib in the indirect comparison. Thus, although the PBS utilisation data cannot support an assessment of effectiveness, it does support a conclusion that the sunitinib trial data are applicable to patients receiving PBS-subsidised sunitinib. This provides some reassurance given a concern that dose reductions due to toxicity might be different between the randomised trial and regular clinical practice in Australia.

The PBAC recalled that it had accepted that its consideration of sunitinib in RCC was influenced by the fact that no effective alternative treatments were available for patients with this disease. This had the effect of accepting a higher incremental cost effectiveness ratio (ICER) and thus a higher price for sunitinib than would have been the case had there been effective alternative treatments. The PBAC noted that this factor, which was relevant for sunitinib, is not relevant for pazopanib because, by definition, sunitinib constitutes an effective alternative treatment for RCC patients.

The PBAC considered that the price of sunitinib in the cost-minimisation analysis needed to both reflect the special pricing arrangements that apply to sunitinib, and also exclude the

increase in price justified with reference to the lack of effective alternative treatments because this justification for a higher price does not apply to pazopanib.

Recommendation:
PAZOPANIB, tablet, 200 mg and 400 mg (as hydrochloride), Votrient®

Restriction:

Authority Required
Initial treatment, as the sole PBS-subsidised tyrosine kinase inhibitor 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 has a WHO performance status of 2 or less.

Note:
Patients who have developed intolerance to sunitinib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised pazopanib.

Patients who have progressive disease with pazopanib are no longer eligible for PBS-subsidised pazopanib.

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

Max quantity: 90 (200 mg)
60 (400 mg)

Repeats: 2

Authority Required
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.

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Note:
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Max quantity:	90 (200 mg) 60 (400 mg)
Repeats:	5

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

GSK welcomes the positive recommendation of the PBAC, as this offers an important treatment choice for patients with stage IV clear cell variant renal cell carcinoma.