Public Summary Document

Product: Pazopanib, film-coated tablets, 200 mg and 400 mg (as hydrochloride), Votrient®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission sought an extension to the recommended Authority required listing to include the initial and continuing treatment of advanced (unresectable and/or metastatic) soft tissue sarcoma (STS) in a patient who meets certain criteria

2. Background

At its March 2012 meeting, the PBAC recommended listing of pazopanib on the PBS as the sole PBS-subsidised therapy for certain patients with renal cell carcinoma on a cost-minimisation basis compared with sunitinb. Listing was effective on the 1st October 2012.

This was the second submission for pazopanib for an extension to the recommended Authority required listing to include initial and continuing treatment of advanced (unresectable and/or metastatic) (STS) in a patient who meets certain criteria.

At its November 2012 meeting, the PBAC rejected the submission on the basis of an unacceptably high ICER. It considered that any re-submission would need to remove inappropriately claimed cost offsets, include costs for management of major recently identified adverse events (e.g. liver failure, MI) and amend the restriction to accurately reflect the trial population.

3. Registration Status

Pazopanib is TGA registered for use in the treatment of advanced and/or metastatic renal cell carcinoma (RCC).

Pazopanib was approved by the TGA as an orphan drug for the treatment of patients with advanced (unresectable and/or metastatic) soft tissue sarcoma on 13 May 2011.

Pazopanib was approved by the TGA for the following additional indication on 20th November 2012:

- Treatment of patients with advanced (unresectable and/or metastatic) Soft Tissue Sarcoma (STS) in patients who, unless otherwise contraindicated, have received prior chemotherapy including an anthracycline treatment. The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma.

4. Listing Requested and PBAC's View

Authority required

Initial treatment, as the sole PBS-subsidised therapy, of advanced (unresectable and/or metastatic) soft tissue sarcoma, in a patient who has a WHO performance status of 2 or less, and have received prior chemotherapy including an anthracycline. Patients with adipocytic STS; gastrointestinal stromal tumour; rhabdomyosarcoma other than alveolar or pleomorphic; chondrosarcoma; osteosarcoma; Ewings tumour/primitive neuroectodermal tumour; dermofibromatosis sarcoma protuberans; inflammatory myofibroblastic sarcoma; malignant mesothelioma; mixed mesodermal tumour of the uterus, and patients who have received prior treatment with angiogenesis inhibitors are not included in the criteria.

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

Continuing treatment beyond 3 months, as the sole PBS-subsidised therapy, of advanced (unresectable and/or metastatic) soft tissue sarcoma 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 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.

The PBAC noted the resubmission excluded first line treatment of pazopanib and the use of pazopanib in patients naïve to angiogenesis inhibitors, consistent with recommendations made in the November 2012 meeting. The PBAC considered the requested listing to be appropriate.

5. Clinical Place for the Proposed Therapy

STS is a relatively uncommon group of malignancies. Current treatment options for STS are usually palliative and include surgery, chemotherapy and radiotherapy. For patients with advanced (unresectable and/or metastatic) STS, who have failed anthracycline treatment as first-line therapy, treatment patterns in second and third line systemic treatment is less clear.

The re-submission proposed that pazopanib, a multi-targeted tyrosine kinase inhibitor, may be considered as an option following anthracycline therapy for treatment of patients with advanced (unresectable and/or metastatic) STS.

6. Comparator

The re-submission nominated a mixed comparator of 50% best supportive care (BSC) and 50% ifosfamide (IFO)/MESNA as the main comparator. This was a revision compared to the previous submission in November 2012, in which the main comparator was BSC, and the

mixed comparator, 70:30 of BSC and IFO, was considered as a complementary option. The PBAC considered that the choice of comparator was not well justified because it depended on a survey of only a small number of clinicians to determine the mix of BSC and ifosfamide. Nevertheless, the PBAC accepted the mixed comparator, noting that the ratio of BSC: ifosfamide was a source of uncertainty.

7. Clinical Trials

The submission presented two trials: (i) VEG110727 comparing pazopanib 800 mg with BSC in 369 patients with advanced STS and (ii) Van Oosterom 2002, a Phase II dose-finding trial, comparing two ifosfamide regimens (3 g/m^2 over 4 hours on three consecutive days vs. 5 g/m^2 as a 24-hour infusion) for first- and second-line line patients (N=76 for second-line treatment). Details of the published trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
VEG110727 [PALETTE]		
Van Der Graaf et al.	Prognostic and predictive factors in advanced soft tissue sarcoma patients treated in an EORTC STBSG global network randomized double blind phase III trial of pazopanib versus placebo (EORTC 62072, PALETTE).	*European Journal of Cancer* (2011); 47 (S1): S662
Van Der Graaf et al.	Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase III trial.	*Lancet* (2012); 379 (9829): 1879-1886
Van Oosterom 2002	Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients.	*European Journal of Cancer* (2002); 38(18):2397-406.

In the clinical trial VEG110727, adult patients were recruited on the basis that they had metastatic STS, and had received up to four prior treatments for advanced disease where no more than two lines have been combination regimens. Other recruitment conditions included (i) WHO performance status of 0-1 and (ii) patients must have failed anthracycline and with no previous treatment with angiogenesis inhibitors.

The re-submission considered the primary outcome of progression free survival (PFS) a more appropriate outcome than overall survival (OS), as PFS is a more robust assessment of efficacy due to the potential confounding in the OS results due to post-trial treatment.

In the Van Oosterom 2002 trial, 182 adult patients (15-75 years) with WHO performance status of 0-1 were recruited on the basis that they had advanced/metastatic STS, of which 76 were in second-line. Other recruitment conditions included (i) locally recurrent disease not amenable to potentially local therapy, (ii) measurable lesions with evidence of progression less than or equal to 6 weeks prior to treatment, and (iii) failed doxorubicin 75 mg/m^2 or epirubicin 150 mg/m^2, discontinued for more than 3 weeks or treatment naïve.

The PBAC noted that the trial population in Van Oosterom was not necessarily consistent with the trial population in VEG110727 and the target PBS population.

In the absence of clinical trials that allow direct and adjusted indirect comparison between ifosfamide and pazopanib using BSC as a common comparator, the re-submission presented an unadjusted (naïve) indirect comparison using VEG110727 and Van Oosterom clinical trial data.

8. Results of Trials

In the trial VEG110727, the primary efficacy outcome was progression free survival (PFS) and a key secondary outcome was overall survival (OS). The Van Oosterom trial investigated time to progression (TTP) and OS amongst other main outcomes.

The re-submission used TTP and PFS interchangeably in the presentation of efficacy results for the Van Oosterom trial although these two outcome measures are not strictly comparable.

As presented in the previous submission, the VEG110727 trial demonstrated that pazopanib resulted in a statistically significant improvement in PFS compared to BSC (HR 0.35; 95% CI: 0.26 to 0.48; p<0.001; median survival pazopanib = 20 weeks (95% CI: 17.9; 21.3) vs. BSC = 7 weeks (95% CI: 4.4; 8.1)). Pazopanib did not result in a statistically significant improvement on OS (HR 0.86; 95% CI: 0.67 to 1.11) p=0.251; pazopanib = 12.5 months (95% CI: 10.6; 14.8) vs. BSC = 10.7 months (95% CI: 8.7; 12.8)).

The PBAC therefore considered that the modelled OS advantage is unlikely to be observed in clinical practice.

The two ifosfamide treatment regimens in second-line in the Van Oosterom trial showed a median TTP of 6 weeks in the 5 g/m^2/day vs. 14 weeks in the 3 g/m^2/3 days (not statistically significant) and a median OS of 10.4 months in the 5 g/m^2/day vs. 8.3 months in the 3 g/m^2/3 days (log rank p=0.43).

The re-submission argued that from a naïve comparison, whilst it would not be possible to draw definitive conclusions, it could be considered that the efficacy outcomes favour pazopanib, with a naïve HR for pazopanib versus ifosfamide. However, the re-submission acknowledges the limitations of the naïve indirect comparison, and therefore uses a more conservative approach of assuming similar efficacy for PFS and OS for pazopanib vs. ifosfamide 3 g/m^2/ 3 days.

Overall, the PBAC agreed that pazopanib is superior to BSC with respect to extending PFS and that this reflected an advantage to patients. The PBAC remained unconvinced that the claim of an extended OS will be seen in clinical practice.

With regard to comparative harm, in the VEG110727 trial, patients in the pazopanib arm were more likely to have adverse events compared to those in the placebo arm. The numbers for serious adverse event was 99/240 (41%) for pazopanib versus 29/123 (24%) for placebo. Adverse events lead to 20% discontinuation in the pazopanib arm, compared to 5% in the placebo arm.

Comparing the two ifosfamide treatment regimens in the Van Oosterom trial, adverse events occurred more often in the 3 g/m^2/3 days compared to the 5 g/m^2/day, especially those related to haematological toxicity. The proportions of patients discontinued due to adverse events were 13% in the 3 g/m^2/3 days arm, as opposed to 3% in the 5 g/m^2/day arm.

The re-submission provided additional data on potential safety concerns beyond those identified in the clinical trials. Most adverse events for pazopanib are associated with hepatic impairment, fatigue, diarrhoea and nausea/vomiting. Most adverse events for ifosfamide are associated with haematological toxicities and urotoxicity.

The re-submission acknowledged that due to different reporting of adverse events between the VEG110727 and Van Oosterom trials, it was not feasible to provide a quantitative comparison of adverse events.

The PBAC considered the comparison of toxicities for pazopanib and ifosfamide was minimally informative given the nature of the indirect comparison.

9. Clinical Claim

The re-submission described pazopanib treatment as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care. This claim was not changed from the previous submission.

The PBAC accepted the claim of superior efficacy in PFS for pazopanib vs. BSC however, considered the claim of superior efficacy in OS for pazopanib vs. BSC inappropriate as there was no statistically significant improvement on the OS depicted in the VEG110727 trial. The PBAC deliberated that the modelled OS advantage is unlikely to be observed in clinical practice. Nevertheless, the PBAC considered that for this disease, the additional PFS would provide a significant advantage for some patients, even without survival benefit.

Comparing pazopanib to ifosfamide (3 g/m^2/3 days), the re-submission concluded that although efficacy outcomes favour pazopanib, the two agents are similarly efficacious and have different safety and tolerability profiles. The PBAC accepted this conclusion.

The PBAC noted the claim of similar efficacy for pazopanib vs. ifosfamide was reasonably conservative, based on data for pazopanib vs. placebo, and given the absence of supportive efficacy data for ifosfamide vs. placebo/best supportive care.

10. Economic Analysis

Similar to the submission in November 2012, the re-submission presented a cost-utility analysis based on:

(i) a superiority claim for comparative benefit and inferiority claim for comparative harms for pazopanib versus BSC, and;
(ii) a claim of similar efficacy and different safety profile for pazopanib versus ifosfamide.

The ICER for pazopanib compared with the mixed comparator (50% BSC + 50% ifosfamide/MESNA was between $45,000 - $75,000 per life year gained, and per QALY.

The majority of efficacy and safety inputs come from the VEG110727 and Van Oosterom trials. The re-submission derived the utility values from VEG110727 and Shingler 2012 and additional rates of adverse events from Lorigan 2007.

The PBAC noted that the economic model was most sensitive to the mix of the proportion of BSC and ifosfamide/MESNA, the extrapolation of the OS curve for pazopanib and ifosfamide using BSC curve parameters, the administration cost of ifosfamide and the ifosfamide dose (3 g/m^2/ 3 days vs. 5 g/m^2/day). A higher administration cost of ifosfamide led to a dominant ICER; whilst, other parameters led to an ICER in the range of $75,000-$105,000.

The PBAC did not consider that the proposed ICER was reliable due to the high unpredictability of the proportion of patients substituting systemic anticancer treatment with pazopanib in both second- and third-line treatment. Additionally, the PBAC noted that the sensitivity analysis shows that the ICER is most sensitive to the comparator ratio. The PBAC considered that the nominated comparator ratio may not be representative of clinical practice, but that accurate data on this issue would not become available.

Compared to the previous submission, the model presented in the re-submission is no longer sensitive to changes in the post-treatment anti-cancer therapy (PTACT) cost, because the same number of average lines of PTACT is applied to all treatment arms.

The PBAC recalled from its previous consideration pazopanib in November 2012 that it did not accept the model of three alternative treatment pathways as being consistent with the proposed clinical algorithm whereby patients progress through anthracycline chemotherapy to pazopanib and then to BSC. The PBAC also noted that the results for OS gain in the PALETTE trial were not statistically significant. These concerns with the economic model were not addressed in the resubmission. Overall, the PBAC reiterated that it did not consider the economic model reliable.

11. Estimated PBS Usage and Financial Implications

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

The estimated cost in the re-submission was approximately 33% less than that of the submission in November 2012, driven mostly by the revision in the total number of patients likely to be treated with pazopanib.

The re-submission estimated the overall net cost to the government health budget of listing pazopanib to be less than $10 million over the five year period, less though in the same range as the previous submission.

The re-submission revised the estimated number of pazopanib patients to be less than 10,000 in year 5, less, though in the same range as the previous submission.

12. Recommendation and Reasons

The PBAC accepted the extension of pazopanib to the recommended Authority required listing to include the initial and continuing treatment of advanced (unresectable and/or metastatic) soft tissue sarcoma (STS) in a patient who meets certain criteria. Although the PBAC noted the unclear, potentially high ICER of pazopanib (due to the indeterminate ratio of the comparator in a practical setting), and the unsupported claim for superior efficacy for OS, the PBAC accepted the submission based on PFS benefit in the context of high unmet clinical need in a population that has limited treatment options and the modest overall cost to the Commonwealth.

The PBAC considered that the aggressive nature of this disease would afford patients limited opportunity to try subsequent lines of therapy, therefore the unmet clinical need for access to therapies for STS with PFS benefit was high.

The PBAC emphasised that it did not consider the economic model to be robust. The PBAC considered that its recommendation of pazopanib was made in the context of high unmet clinical need for a small number of patients, with a modest overall financial impact.

The PBAC recommended that Authority applications for initial treatment should be in writing, and continuing treatment should be authorised by telephone.

The PBAC recommended that pazopanib is not suitable for prescribing by nurse practitioners.

The PBAC requested that the Department review the utilisation of pazopanib in five years.

Outcome:
Recommended

Recommended listing:
(To be finalised)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name	Manufacturer
PAZOPANIB HYDROCHLORIDE				
Tablet 200 mg	90	2	Votrient	GK
Tablet 400 mg	60	2	Votrient	GK

Severity:	Advanced (unresectable and/or metastatic)
Condition/Indication:	Soft tissue sarcoma

Treatment phase:	Initial treatment
Restriction:	Authority required - In Writing
Clinical criteria:	Patient must have a WHO performance of 2 or less AND Patient must have received prior chemotherapy treatment including an anthracycline AND Patient must not have received prior treatment with an angiogenesis inhibitor AND The treatment must be the sole PBS-subsidised therapy
Prescriber Advice:	Patient must not have any of the following conditions: • Adipocytic soft tissue sarcoma • Gastrointestinal stromal tumour (GIST) • Rhabdomyosarcoma other than alveolar or pleomorphic • Chondrosarcoma • Osteosarcoma • Ewings tumour/primitive neuroectodermal tumour • Dermofibromatosis sarcoma protuberans • Inflammatory myofibroblastic sarcoma • Malignant mesothelioma • Mixed mesodermal tumour of the uterus
Administration Advice:	NOTE: No applications for increased maximum quantities and/or repeats will be authorised.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name	Manufacturer
PAZOPANIB HYDROCHLORIDE				
Tablet 200 mg	30	5	Votrient	GK
Tablet 200 mg	90	5	Votrient	GK
Tablet 400 mg	30	5	Votrient	GK
Tablet 400 mg	60	5	Votrient	GK

Severity:	Advanced (unresectable and/or metastatic)
Condition/Indication:	Soft tissue sarcoma
Treatment phase:	Continuing treatment beyond 3 months
Restriction:	Authority required - Telephone

Clinical criteria:	Patient must have previously been issued with an authority prescription for pazopanib, AND The treatment must be the sole PBS-subsidised therapy AND Patient must have stable or responding disease according to *Response Evaluation Criteria In Solid Tumours (RECIST)* AND Patient must require dose adjustment *(applicable to listings with max qty. 30, No. of rpts. 5)*
Definitions:	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.
Administration Advice:	NOTE: No applications for increased maximum quantities and/or repeats will be authorised.

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 welcomes the positive recommendation of the PBAC, as this offers an important treatment choice for patients with advanced soft tissue sarcoma.