



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Pazopanib hydrochloride

Proprietary Product Name: Votrient

Sponsor: GlaxoSmithKline Australia Pty Ltd

February 2013

TGA Health Safety
Regulation

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I. Introduction to product submission

Submission details

<i>Type of Submission</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	30 August 2012
<i>Active ingredient:</i>	Pazopanib hydrochloride
<i>Product Name:</i>	Votrient
<i>Sponsor's Name and Address</i>	GlaxoSmithKline Australia Pty Ltd Level 4, 436-438 Johnston Street Abbotsford VIC 3067
<i>Dose form:</i>	Tablet
<i>Strengths:</i>	200 mg and 400 mg
<i>Container:</i>	Bottle
<i>Pack sizes:</i>	30 or 60 (400 mg strength); 30 or 90 (200 mg strength)
<i>Approved Therapeutic use:</i>	For the treatment of 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.
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	800 mg once daily
<i>ARTG Number</i>	161282, 161281

Product background

Pazopanib inhibits the tyrosine kinase activities of vascular endothelial growth factor receptors (VEGFR)-1, -2 and -3, platelet-derived growth factor (PDGFR)- α and - β , and stem cell factor receptor (c-Kit). It is currently registered for *the treatment of advanced and/or metastatic renal cell carcinoma (RCC)*. Its efficacy as an anti-cancer agent is thought to be due to inhibiting angiogenesis mediated through the above receptor systems.

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (the sponsor) to extend the approved indications for Votrient to include the following:

“Treatment of patients with advanced (unresectable and/or metastatic) Soft Tissue Sarcoma (STS) who have received prior anthracycline treatment or for patients who are unsuited for such therapy.

The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma.”

The proposed dose for the treatment of STS is 800 mg daily, which is the same as that currently indicated for RCC. No changes are proposed to the product formulation or range.

Orphan drug status for Votrient when used for the proposed indication was granted in May 2011.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in June 2010, for use in the treatment of RCC.

At the time of the current application, pazopanib for the treatment of STS was approved in the US (in April 2012), Ecuador and the Philippines, and was under evaluation in 10 other countries. A positive opinion for a similar application in the European Union (EU) was given by the European Medicines Agencies (EMA's) Committee for Medicinal Products for Human Use (CHMP).

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

Limited nonclinical data were submitted to directly support this application, but additional animal studies are not required given that efficacy will rely on clinical data and that the toxicity profile associated with the proposed dose (800 mg/day) has been adequately assessed in nonclinical studies submitted previously.

Assessment

The sponsor indicates that a number of nonclinical studies not previously submitted to the TGA have been conducted to support the use of pazopanib for various (currently unapproved) indications. Only a study of limited relevance for the use of STS in adults was submitted for this application; presumably other studies will be submitted for future applications as relevant. It is notable that a submitted study in mice with human liposarcoma (see below for study details) does not directly support this application, since the proposed indication states that *‘The Phase III trial population excluded patients with ... adipocytic soft tissue sarcoma.’*

The studies in juvenile animals submitted for this application are not of direct relevance since pazopanib is not indicated or proposed for use in children. It would be expected that these, along with any other supporting nonclinical data, would be re-submitted for evaluation to support any future application that includes use in children.

Juvenile rat studies to support clinical trial use of pazopanib in children

Nonclinical studies provided with this application have been conducted to support the on-going clinical development of pazopanib in children and as part of a Paediatric Implementation Plan approved in the EU. Juveniles received pazopanib for various durations over age 9 days to 62 days; only the main study was compliant with requirements for good laboratory practices. Exposure of rats from these studies is shown in Table 1, below (previous data from adult rats are included for comparison).

Table 1. Exposure to pazopanib in animal studies

Rat age; study duration or no. of doses; (study No.)	Doses (mg/kg/day)	C _{max} (µg/mL)	AUC _{0-24 h} (µg.h/mL)
<i>*Adult; 4 weeks (G01200)</i>	<i>3, 10, 30, 100, 300</i>	<i>10, 25, 40, 32, 47</i>	<i>69, 174, 293, 216, 365</i>
<i>*Adult; 26 weeks (R41150)</i>	<i>3, 30, 300</i>	<i>10, 53, 81</i>	<i>88, 459, 858</i>
Juvenile (13 days); 5 doses (D10051)	0.3 , 3, 30, 300, 1000	1 , 6, 29, 38, 30	16 , 98, 408, 624, 314
Juvenile (35 days); 27 doses (D10051)	0.3 , 3	0.2 , 2.2	1.8 , 15
Juvenile (25 days); 5 doses (D10051)	30 , 300, 1000	17 , 80, 65	153 , 805, 815
Juvenile (35 days); 15 doses (D10051)	30 , 300, 1000	30 , 61, 61	212 , 620, 611
Juvenile (13 days); 5 doses (I10194)	10, 100	10, 23	166, 402
Juvenile (25 days); 5 doses (G10052)	10 , 30, 300	7.5 , 25, 77	51 , 155, 590
Juvenile (35 days); 15 doses (G10052)	10 , 30, 300	10 , 27, 67	93 , 214, 732
Juvenile (62 days); 42 doses (**except at HD); (G10052)	10, 30, 100	15, 30, 46	121, 202, 482

*Mean male and female data from previously evaluated studies. **100 mg/kg/day was given on Post-Partum (PP) days 52 to 61; these pups had previously received 300 mg/kg/day on PP days 21-48.

Bolded values indicated No Observed Effect Levels (NOELs).

Exposures (maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve over 24 h (AUC_{0-24h})) at all doses in all rat studies shown in the Table above are generally lower than those expected in humans (C_{max} of 58.1 µg/mL and AUC_{0-24h} of 1037 µg.h/mL in a 50 kg adult receiving 800 mg/day pazopanib; from clinical Study VEG10007, as stated in the sponsor's summary information). While a comprehensive comparison of pharmacokinetics (PK) between juveniles and adults has not been made, it appears that exposure for a given dose does not greatly differ between pups and adult rats.

Treatment of rat pups with pazopanib in the early post-partum period was generally fatal and was associated with toxicities to all major organ systems except brain. Toxic effects were associated with reduced cell proliferation and increased cell death in the heart, liver, lung and kidneys, and additional changes to various renal cells.

A study in adult rats did not shed light on precise molecular mechanisms underlying pazopanib-induced liver toxicity.

Older rats were less susceptible to the fatal developmental toxicities than younger pups; although the older rats remained more susceptible to pazopanib-induced toxicity when compared with adults.

At most, the studies in juveniles support the careful on-going clinical trial of pazopanib in children aged >2 years.

Nonclinical summary and conclusions

- Nonclinical data relevant to this application comprised one efficacy study in a mouse model of human liposarcoma and two hepatotoxicity studies. The lack of additional toxicity studies is acceptable given that the proposed dose (800 mg/day) for the treatment of STS is the same as that for the currently approved indication (RCC) and therefore previously identified toxicity issues remain applicable.
- The sponsor has also submitted three studies in juvenile rats conducted to support the on-going clinical development of pazopanib for use in children. Information from these studies is proposed to be included in the proposed (revised) PI (see below).
- The single animal efficacy study showed that PO treatment with 30 or 100 mg/kg pazopanib once or twice daily delayed the growth of human liposarcomas implanted in immune-compromised mice, with the effect being dependent on dose but apparently not on dosing frequency. Decreases in tumour volume were accompanied by profound decreases in body weight. The efficacy of pazopanib (and the effect on weight) in mice reversed over a 7 day treatment-free period but recurred when treatment resumed.
- This study tends to support the proposal that pazopanib may be efficacious for the treatment of STS; however it is noted that patients with adipocytic STS were not included in the Phase III population relevant to this application (see sponsor's proposed indication, above). The lack of more relevant and comprehensive nonclinical efficacy studies is accepted given that demonstration of efficacy will be based on clinical data.
- Pazopanib-associated hepatotoxicity, which is the subject of a boxed warning in the PI¹, was investigated in a 1 week repeat dose toxicity study in adult male rats which included *ex vivo* gene expression assays; and in an *in vitro* study investigating potential for the effects on the hepatic sodium-taurocholate cotransporting polypeptide and the

¹ A boxed warning is a succinct warning statement printed at the start of the approved PI, designed to alert prescribers to an important safety issue with a medicine. The warning is highlighted by a bold black surround or "box".

bile salt export transporters in human and rat hepatocytes. Neither of these shed light on possible mechanisms underlying hepatotoxicity with pazopanib.

- Pazopanib is not currently recommended or proposed for use in children. However, studies have been conducted in juvenile rats to support the on-going clinical development of pazopanib for the treatment of STS in a paediatric population. These showed a profound adverse effect on the growth and development of the major organ systems (kidneys, heart, lung, liver) and associated deaths when treatment started soon after birth. Decreased cellular proliferation and/or increased apoptosis were found in all organs investigated (heart, kidneys, liver and lung) except brain.
- Effects on organ development were considered to be a result of adverse effects on organ vasculogenesis and glomeruli as a result of (pharmacologically) mediated inhibition of the VEGF signalling by pazopanib. These findings suggest that pazopanib interferes with VEGF-dependent glomerular maturation as well as organ growth and development of kidney, heart, liver, and lung in preweanling juvenile rats.
- Older rats (aged ≥ 21 days) were less sensitive to the fatal developmental toxicities associated with pazopanib; the toxicity profile in these pups was similar to that found previously in adult rats, with major target organs for toxicity being the bones, teeth, kidneys, gastrointestinal system and male reproductive system. However, juveniles appear to be more sensitive to pazopanib induced toxicities than adults, since the range of effects observed after 6 weeks' treatment of young rats was seen only in the longer duration studies (≥ 13 weeks) in adults, with the same doses. Further, deaths occurred in the juveniles but not in the older rats at the same dose level. These differences do not appear to be associated with differences in exposure to pazopanib for a given dose.

Recommendation

While no relevant animal efficacy studies and only limited additional toxicity studies have been provided, these are not required for this application and therefore there are no objections on nonclinical grounds to the registration of pazopanib for the treatment of STS. Amendments to the PI to include details of findings in juvenile rats should not be approved.

IV. Clinical findings

A summary of the clinical findings is presented in this section. The full clinical findings can be found in Attachment 2.

Introduction

Background and rationale

Pazopanib is a potent tyrosine kinase inhibitor (TKI) and despite heterogeneity of various STS these tumours have been shown to have a commonality in that high levels of VEGF gene expression have been observed in many STS subtypes. Furthermore, circulating VEGF levels are higher in patients with advanced STS and are associated with the histological Grade of the tumour. Other mediators of angiogenesis such as PDGF have also been shown to be expressed in STS and are correlated with higher tumour Grade and increased cell proliferation. Accordingly, this represents an appropriate rationale for evaluation of TKIs in the treatment of advanced stage STS.

Scope of the clinical dossier

The submission contains the appropriate materials in regards to summaries of clinical information and literature references. The submission included full clinical study reports in relation to the two principal studies for assessment, namely the pivotal Phase III, randomised, controlled trial, Study VEG110727, and a supportive Phase II trial, Study VEG20002. There is also an additional study examining thromboembolic events in STS patients (Study WEUSRTP4987).

Paediatric data

There are no specific paediatric clinical data in the submission.

Good clinical practice

All aspects of good clinical practice have been observed.

Pharmacokinetics**Studies providing pharmacokinetic data**

Full PK data for pazopanib after single and repeated oral dose administration for patients with cancer were provided in the original regulatory submission in relation to advanced stage RCC.

Additional PK data for pazopanib in adult subjects with STS after repeated oral doses of pazopanib are provided in the supportive study VEG20002, which is a Phase II, multicentre, open label, non-randomised study evaluating the therapeutic activity, safety and tolerability of pazopanib in subjects with four of the most common types of STS, including leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and other eligible types of STS, who had relapsed following standard therapies or for whom no standard therapy existed. Patients received oral pazopanib 800 mg once daily until disease progression or unacceptable drug related events, any recurrent illnesses preventing further drug administration, or subject refusal. Pazopanib dose reductions were allowed during the study.

Evaluator's overall conclusions on pharmacokinetics

The data from the Phase II Study VEG20002 demonstrates the plasma pazopanib concentrations were maintained above the level associated with biologic effects consistent with VEGFR inhibition in more than 70% of patients for whom data were available, similar to those observed in patients with RCC in study VEG102616. These results therefore indicated that pazopanib 800 mg once daily is an appropriate monotherapy dose for patients with STS and provides optimal biologic effect associated with VEGFR inhibition and clinical effects.

Pharmacodynamics

No new data regarding pharmacodynamics is provided in this submission.

Efficacy**Dosage selection for the pivotal study**

The data indicated in the PK section regarding Study VEG20002 in patients with advanced stage STS who received pazopanib 800 mg daily demonstrates that the pazopanib 800 mg

once daily dosage is an appropriate monotherapy for patients with STS and provides optimal biologic effects associated with VEGFR inhibition and clinical effects. Accordingly, a dose of 800 mg pazopanib per day represents an appropriate dosage selection for the pivotal studies.

Summary of studies

The primary evidence to support the clinical efficacy of pazopanib in advanced STS is provided by the pivotal Phase III Study VEG110727. Supportive data is provided from the Phase II open label study, VEG20002. Clinical design features, study population and efficacy endpoints are summarised below in Table 2.

Table 2. Summary of efficacy studies

Study	VEG110727	VEG20002
Level of Evidence	Pivotal	Supportive
Critical Design Features	Phase III Randomized (2:1) ^a Double-blind Placebo-controlled	Phase II Non-randomized Open-label Single-arm
Study Population	Metastatic STS with confirmed disease progression during or following therapy (up to 4 prior lines of systemic treatment for advanced disease). Progression within 6 months of prior therapy for advanced disease or within 12 months of neoadjuvant/adjvant therapy Disease progression on or after anthracycline-based regimen WHO PS 0 or 1 -Leiomyosarcoma -Synovial sarcoma -Other types of STS (excluding GIST and adipocytic STS)	Advanced and/or metastatic STS that was refractory or relapsed (no more than 1 combination or two single agents of chemotherapy regimen for advanced disease); Objective progression within the last 6 months WHO PS 0 or 1 -Leiomyosarcoma -Synovial sarcoma -Adipocytic tumors -Other types of STS (excluding GIST).
Number of subjects	369 subjects Pazopanib: 246 Placebo: 123	142 subjects
Efficacy endpoints		
Primary	PFS by independent radiologist	PF rate at Week 12 by peer* and investigator review
Secondary	OS (principal); ORR; Duration of response, Time to response	PFS OS ORR Duration of response, Time to response

VEG110727 was a pivotal Phase III, randomised, double blind, placebo controlled, multicentre, international study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) in collaboration with GlaxoSmithKline (GSK).

The primary objective of the study was to evaluate and compare progression free survival (PFS) in pazopanib versus placebo treated patients. The principal secondary objective was to evaluate and compare overall survival (OS) in the two treatment arms. Other secondary objectives were to evaluate PFS in the three histology subtypes, that is, leiomyosarcoma, synovial sarcoma and other STS eligible histologies recruited onto the study. The study also compared the two treatment arms for overall response rate (ORR), time to response, and duration of response, and assessed safety and tolerability.

The supportive trial VEG20002 was a Phase II, multicentre, open-label, non-randomised study conducted by the EORTC and supported by GSK. The purpose of the study was to evaluate the activity and tolerability of pazopanib in patients with relapsed or refractory STS for whom no standard therapy existed. The patients entered onto the study received oral pazopanib at a dose of 800 mg once daily until disease progression, unacceptable drug

related events, intercurrent illnesses preventing further drug administration, or subject refusal.

Evaluator's conclusions on clinical efficacy for the proposed indication.

VEG110727: The data from this quite robust study has clearly indicated a significant advantage in terms of PFS for those patients receiving pazopanib as second or later line therapy in the patients with advanced stage STS. This result was applicable across the various histological subtypes as well as other stratification factors, and was also applicable in relation to appropriate sensitivity and subgroup analyses. It is noteworthy that despite this benefit, OS analyses did not show a significant difference for the pazopanib versus placebo arms. The differences in terms of proportion of patients receiving subsequent therapy may have an influence on this, but at this time, the level of benefit for pazopanib appears to be modest. There would be value for the evaluation of pazopanib as an earlier treatment in patients who have advanced and metastatic STS.

VEG20002: The data show a modest level of response to pazopanib in these patients, the most sensitive subgroups being leiomyosarcoma and synovial sarcoma patients. It is noteworthy that PFS for these two groups of patients was similar to that observed in the pivotal trial. This therefore lends some degree of support to the data from the principal study.

Quality of Life

The data from the Quality of Life (QoL) analyses are limited in their value partly because of the significant proportion of patients receiving placebo who did not undergo assessment on weeks 8 and 12 because of progressive disease, thereby reducing the potential utility of this assessment. A greater decline in QoL seen in patients receiving pazopanib in the assessment relates to side-effects associated with pazopanib and therefore this might be anticipated. Nevertheless, these changes appear to be relatively small and it was the opinion of the investigators that they were not clinically significant.

Safety

Studies providing evaluable safety data

This review of safety for those patients receiving pazopanib for the treatment of advanced stage STS arise from the two principal studies presented in this submission, namely the pivotal Study VEG110727 and the supportive trial VEG20002. A total of 382 patients who received pazopanib in these two studies provide the safety data evaluated. In the main, the safety data are presented as an integrated evaluation of these two studies with certain elements of the pivotal trial emphasised. The safety population was all patients who had received at least one dose of investigational agent. Data from the therapy period is defined as the time from the first dose of randomisation medication to 28 days post last dose of medication. The safety data for the pivotal study is based on the clinical cut-off date of 22 November 2010 and for the supportive study 20 August 2010.

Post marketing safety data, and data on thromboembolic events in STS patients from Study WEUSRTP498 were also reviewed.

Evaluator's overall conclusion on clinical safety

The safety data presented from the two study populations with advanced stage STS treated with pazopanib essentially show toxicities similar to that previously observed in studies with RCC. These included fatigue, diarrhoea, nausea, decreased weight and hypertension. More serious toxicities, such as hepatotoxicity, arterial thromboembolic

events, haemorrhagic events, bowel perforations and fistulae, have been previously identified, as has myocardial dysfunction. Only a small proportion of these adverse events (AEs) reached Grade III or IV in intensity, including a small number of cases of fatigue, hypertension, dyspnoea and diarrhoea.

The incidence of more significant toxicities, including hepatotoxicity previously well described among the RCC patient population, demonstrated a somewhat similar incidence in these STS studies, with two patients dying with hepatic failure in conjunction with other clinical events.

The incidence of myocardial dysfunction appeared to be perhaps a little higher in these studies, which may relate to the previous exposure to anthracyclines for the vast majority of these patients. Nevertheless, there is a requirement for careful monitoring of these patients, with appropriate evaluations of left ventricular ejection fraction (LVEF) both at baseline and regular intervals throughout treatment thereafter.

The increased incidence of venous thromboembolic phenomena in this STS population appears, in part, to be related to the overall general medical condition of the patient population. Nevertheless, in patients with advanced stage STS, caution is required in the administration of pazopanib, as well as appropriate monitoring. The new signal of pneumothorax appears to be a phenomenon associated with necrosis of tumour nodules in the lung, but again this requires relevant monitoring.

In summary, the overall safety profile of pazopanib in this STS patient population appears to be generally manageable with relevant monitoring and early intervention as required.

List of questions

None.

First round clinical summary and conclusions

Benefit risk assessment

First round assessment of benefits

Data provided from the pivotal study VEG110727 in patients with advanced metastatic STS of various histological subtypes who had previously received at least one line of chemotherapy in the advanced disease setting demonstrates pazopanib results in a statistically significant improvement in PFS, compared to placebo. The study was generally well conducted and quite robust in terms of numbers entered onto the trial. The spectrum of sarcomas evaluated was relatively broad, with evidence of worthwhile benefit being observed across the various histological subtypes. There was significant improvement in PFS, supported by a modest but definite benefit in response rate, together with a significant benefit in duration of response. There was, however, an insignificant difference in OS data for the two groups of patients. This may in part be due to the somewhat higher proportion of patients in the placebo group receiving subsequent treatment following progression; but nevertheless is indicative of the fact that pazopanib in this setting exerts a modest degree of benefit. Nevertheless, as these patients were heavily previously treated and there is a paucity of agents available for the management of STS, it seems appropriate to support pazopanib as a new agent for the treatment of advanced stage STS.

In regards to the proposed indication for patients with advanced STS of no specific histological subtype, there is support from the evidence of the pivotal study in which the various histological subtypes evaluated all showed benefit in terms of significant improvement in PFS.

In regards to the supportive trial, this provides limited evidence of further benefit for pazopanib, but nevertheless the time to disease progression in this study was comparable to that from the pivotal trial, thereby supporting the data. It is worth commenting that as a result of this study, patients with adipocytic tumours were excluded from the pivotal study. Nevertheless, review of the data for the adipocytic tumour type would suggest that there is modest responsiveness in these patients and therefore the evaluator does not see any particular reason to exclude them for potential benefit from a trial of pazopanib.

First round assessment of risks

The overall safety profile of pazopanib demonstrated from the two STS trials is generally comparable with that previously observed in patients with advanced stage RCC for which pazopanib has now been approved for usage. The overall incidence of adverse effects including the most common (such as fatigue, diarrhoea, nausea, decreased weight and hypertension) were most often Grades I and II, with limited numbers of more severe Grades. The more significant toxicities, including hepatotoxicity, myocardial infarction and venous thromboembolism, certainly warrant careful monitoring, but nevertheless, in general terms, relevant management should minimise major adverse sequelae.

The new safety signals arising from the studies of the STS patients in relation to increased incidence of venous thromboembolism and pneumothorax, as well as a clearer understanding of the potential for myocardial dysfunction, are all clearly signalled in the proposed PI, with appropriate caution being advised as a result.

First round assessment of benefit-risk balance

The benefits observed from the pivotal trial together with the data from the supportive study have certainly indicated a significant benefit in terms of PFS for pazopanib in patients with advanced and heavily previously treated STS. The benefit seems to range across all the relevant histological subtypes. The degree of benefit observed is modest, but as the patient population was heavily previously treated, this nevertheless represents evidence of worthwhile benefit warranting appropriate consideration for inclusion of pazopanib in the treatment armamentarium of advanced stage STS.

The safety profile and levels of severity observed from these studies are generally commensurate with those seen from earlier trials. The new safety signals of pneumothorax and an increased incidence of venous thromboembolism have been clearly delineated and relevant statements made in the draft PI.

In relation to an earlier agent, trabectedin², which was previously evaluated and proposed for rejection for the treatment of patients with STS, the evaluation demonstrated that the level of benefit for trabectedin in STS was very small and the overall spectrum of toxicities associated with trabectedin considerable. Accordingly the benefit-risk balance was insufficient to support its recommendations. The evaluator does not consider that the evidence from trabectedin has an adverse influence for pazopanib, which has shown a somewhat greater degree of benefit and, most importantly, a lesser range and extent of adverse effects.

Accordingly the evaluator considers the benefit-risk balance is supportive of approval of pazopanib for the treatment of patients with advanced stage STS.

Recommendation regarding authorisation

On the basis of the evaluation discussed above, the evaluator considers that it is appropriate to support approval for the additional indication for pazopanib, that is, for the

² The mechanism of action of trabectedin is believed to relate to the way in which it binds to deoxyribonucleic acid (DNA). The AusPAR for trabectedin is available at <<http://www.tga.gov.au/pdf/auspar/auspar-yondelis.pdf>>

treatment of patients with advanced (unresectable and/or metastatic) STS who have received prior anthracycline treatment or for patients who are unsuited for such therapies.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor was considered acceptable and is shown in Table 3.

Table 3. Ongoing safety concerns.

Important identified risks	<ul style="list-style-type: none"> -Hepatic dysfunction -Pulmonary haemorrhage -GI bleeding -Cerebral haemorrhage -GI perforation and fistula -Cardiac arrhythmias -Cardiac ischaemia -Cerebrovascular ischaemic events -Hypertension -Hypothyroidism -Diarrhoea -Fatigue/Asthenia -Hypoglycaemia -Impaired Healing -Proteinuria -Thrombocytopenia -Leukopenia and Neutropenia -Cardiac dysfunction -Venous thromboembolic events -Pneumothorax -Inhibition of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) by co-administered drugs
Important potential risks	<ul style="list-style-type: none"> -Drug interactions with substrates of cytochrome P450 -Drug interactions with inhibitors of CYP3A4 -Food effect -Concomitant treatment with inducers of CYP3A4 -Drug interactions with substrates of P-gp and BCRP. -Drug interactions related to inhibition of human organic anion transporting polypeptide by pazopanib -Concomitant use of pazopanib and simvastatin (Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A) -Reproductive effects -Potential for carcinogenicity -Adult Off-Label Use -Paediatric Off-Label Use
Important missing information	<ul style="list-style-type: none"> -Use in patients with severe hepatic dysfunction

Pharmacovigilance plan

Routine and additional pharmacovigilance activities are in place for the previously evaluated RCC indication. Routine and additional pharmacovigilance activities are proposed to monitor all safety concerns for the STS indication.

Additional pharmacovigilance activities are summarised in Table 4.

Table 4. Additional pharmacovigilance activities.

Ongoing safety concern	Assigned additional pharmacovigilance activity
Important potential risks Drug interactions with inhibitors of CYP3A4 Potential for Carcinogenicity Paediatric Off-Label Use	-Study VEG113971 -Two-year carcinogenicity studies in rats and mice -Paediatric Investigation Plans have been submitted to the EU for soft tissue sarcoma/Study ADVL0815 -NCI study ADVL0815
Important missing information Use in patients with severe hepatic dysfunction	-NCI study 8063 is in progress.

Routine and the ongoing additional pharmacovigilance activities are considered to be acceptable. The sponsor states that studies VEG113971 and NCI 8063 will be reported, when available, in Periodic Safety Update Reports (PSURs). Paediatric Investigational Plans have been submitted to the EU, however paediatric use is expected to be minimal in the Australian context.

Risk minimisation activities

The sponsor concludes that only routine risk minimisation activities are necessary to mitigate the safety concerns associated with Votrient. The sponsor's justifications are accepted and routine risk minimisation activities are considered sufficient.

The evaluator suggested revisions to PI statements in the context of the risk minimisation activities; details of these are beyond the scope of this AusPAR.

Summary of recommendations

It is recommended that the Delegate:

- Implement RMP Version TBA, data lock point 01 February 2011, including the sponsor's response to the requests from the OPR for information/documents and any future updates, as a condition of registration.

Revisions to the proposed PI were also recommended. Details of these are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There were no objections to the extension of indication from the nonclinical evaluator. See below under *Paediatric Use* for discussion of juvenile rat studies in the context of statements in the proposed PI concerning paediatric use.

Clinical

Overview of data

Three studies were submitted, as described in Table 5.

Table 5. Summary of submitted studies.

<p>Pivotal VEG110727 (PALETTE)</p>	<p>A Phase III, randomised, double-blind, placebo-controlled trial in patients with various types of metastatic STS (not gastrointestinal stromal tumours or adipocytic sarcomas) whose disease had progressed during or following prior therapy.</p> <p>This study has been published³, accompanied by an editorial by Vivien Bramwell⁴ (who has been on a Canadian advisory board for the sponsor for pazopanib).</p>
<p>Supportive VEG20002</p>	<p>A Phase II, open-label, non-randomised study in subjects with relapsed or refractory STS, for whom no standard therapy existed.</p> <p>This study has been published⁵.</p>
<p>Other WEUSRTP4987</p>	<p>Observational study of thromboembolic events in STS patients.</p>

Pharmacokinetics

Results from VEG20002 indicated that the PK of pazopanib in subjects with sarcoma is similar to the PK of pazopanib in subjects with RCC.

In VEG20002, only 74 of 142 patients contributed to the PK analysis. The summary data indicate wide inter-subject variability (for example, pre-dose on day 29, the median pazopanib concentration was 33.2 ng/mL, but the range was 5.43-104 ng/mL), but also suggest little fluctuation from trough levels after dosing occurs at steady state (for example, post-dose on day 29, the time to maximum concentration (T_{max}) was at 3-4 h with median C_{max} 46.2 ng/mL).

Based on “trough pazopanib concentrations associated with one half of the maximum effect in two concentration-effect relationships” the sponsor has arrived at a value of 20 ng/mL as the threshold for concentrations associated with biological effect (apparently meaning effects consistent with VEGFR inhibition). In VEG20002, 55/74 subjects (74%) had a day 29 pre-dose concentration of ≥ 20 ng/mL (and 79% at day 85 pre-dose).

In a cross-study comparison with VEG102616 (Phase II study in RCC, that used an identical blood sampling scheme), it was noted that mean pazopanib concentrations from VEG20002 (STS study) were greater than mean values from VEG102616 (RCC study) at all time-points. For example, in STS subjects (VEG20002), pre-dose on day 29, the mean

³ van der Graaf WT, Blay JY, Chawla SP *et al.* Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet* 2012;379:1879-1886.

⁴ Bramwell V. Pazopanib and the treatment palette for soft-tissue sarcoma. *The Lancet* 2012;379:1854-1856.

⁵ Sleijfer S, Ray-Coquard I, Papai Z *et al.* Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol* 2009;27: 3126-3132.

pazopanib concentration was 37.1 ng/mL; in RCC subjects (VEG102616) the mean was 28.2 ng/mL, that is, 24% lower. There also tended to be greater variability in the STS study, perhaps reflecting smaller sample size or heterogeneity of STS.

Attention should be paid to (a) potential heterogeneity of efficacy (and safety) outcomes, and (b) the safety profile in STS, as exposure may be higher than in RCC.

Pharmacodynamics

There were no new pharmacodynamics data.

Efficacy

The pivotal source of efficacy evidence in this submission was VEG110727.

Study VEG110727 (PALETTE)

VEG110727 was a Phase III, randomised, double-blind, placebo-controlled trial in patients with metastatic STS whose disease had progressed during or following therapy.

Eligible patients were 18 years of age or older, with metastatic STS regardless of Grade (Table 6, below, shows a slight tumour Grade imbalance). Patients had progressive disease according to RECIST⁶ criteria compared with prior disease assessment within 6 months (12 months for patients who only had prior systemic adjuvant therapy). Patients had a poor prognosis.

⁶ Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumour response with X-ray, computer tomography and magnetic resonance imaging.

Table 6. Summary of tumour description (VEF110727 intention to treat population).

Tumor type ^a	Tumor subtype ^a	Number (%) of Subjects	
		Placebo (N=123)	Pazopanib (N=246)
Smooth muscle tumors	Leiomyosarcoma (excluding skin)	49 (40)	109 (44)
Tumours of uncertain differentiation	Synovial sarcoma	13 (11)	25 (10)
	Epithelioid sarcoma	5 (4)	7 (3)
	Alveolar soft part sarcoma	4 (3)	6 (2)
	Desmoplastic small round cell tumour	1 (<1)	3 (1)
	Clear cell sarcoma	2 (2)	1 (<1)
	Extra-renal rhabdoid tumor	0	1 (<1)
	Neoplasms with perivascular epithelioid cell differentiation (PEComa)	0	1 (<1)
	PNET/Extraskeletal Ewing tumor	2 (2)	0
Fibroblastic	Myxofibrosarcoma	6 (5)	8 (3)
	Solitary fibrous tumor	4 (3)	8 (3)
	Sclerosing epithelioid fibrosarcoma	0	3 (1)
	Adult fibrosarcoma	0	2 (<1)
	Low grade fibro myxoid sarcoma/hyalinizing spindle cell tumor	0	1 (<1)
So-called fibrohistiocytic tumors	Undifferentiated pleomorphic sarcoma (pleomorphic MFH)	11 (9)	20 (8)
	Undifferentiated pleomorphic sarcoma with giant cells (giant cell "MFH")	0	1 (<1)
Undifferentiated sarcoma NOS	N/A	5 (4)	15 (6)
MPNST	N/A	4 (3)	8 (3)
Vascular tumors	Angiosarcoma	3 (2)	3 (1)
	Epithelioid hemangioendothelioma	0	1 (<1)
Skeletal muscle tumors (rhabdomyo-sarcoma)	Embryonal (incl spindle cell, botryoid, anaplastic)	1 (<1)	0
	Alveolar rhabdomyosarcoma (incl solid anaplastic)	1 (<1)	0
Adipocytic (liposarcoma)	Dedifferentiated	0	1 (<1)
Pericytic	Malignant glomus tumor	1 (<1)	0
Chondro-osseous tumors	Extraskeletal osteosarcoma	1 (<1)	0
Other	N/A	10 (8)	22 (9)

Data Source: VEG110727 Table 6.3000

MFH: malignant fibrous histiocytoma; MPNST: malignant peripheral nerve sheath tumors; N/A: Not applicable; NOS: not otherwise specified; PNET: Primitive neuroectodermal tumor

a. Tumor type and tumor subtype are from the WHO classification of soft tissue sarcoma 2002 (modified June 2008) (VEG110727 RAP)

Note: Tumor type and tumor subtype are reported from the central review data unless the review was not conducted. If the review was not conducted, the local pathologist assessment has been used. Subjects without the tumor type of Leiomyosarcoma or Synovial sarcoma are included in the "other" STS histologies ITT population

Progressive disease was, in large part, despite systemic therapy for metastatic disease (at least one regimen containing an anthracycline; a maximum of four lines; a maximum of two lines of combination regimens). Previous treatment with angiogenesis inhibitors (excluding mammalian target of rapamycin (mTOR) inhibitors) or VEGF/VEGFR-targeting agents was not allowed.

Acceptable organ function and performance status were required. Detailed exclusion criteria are outlined in the PALETTE publication by van der Graaf *et al*, on page 1880⁷.

A total of 369 subjects were randomised (2:1) to receive oral pazopanib (800 mg once daily) or placebo, after stratification by performance status and number of lines of prior therapy. There was no subsequent cross-over. These 369 patients (246 pazopanib, 123 placebo) made up the intention to treat (ITT) population.

Demographic characteristics were broadly comparable between arms. Median age in the placebo group was 51.0 years, and in the pazopanib group 56.0 years. Placebo arm subjects were slightly heavier (medians 73.0 kg and 69.0 kg), which is potentially relevant for a drug associated with weight loss.

Leiomyosarcoma excluding skin (40% of placebo subjects and 44% of pazopanib subjects) and synovial sarcoma (11% and 10% respectively) were the two commonest STS types; there were more than 23 further tumour types identified in enrolled patients. In other words, there was heterogeneity with regard to STS type, although the two arms were comparable in this regard. Notable exclusions were adipocytic sarcomas, gastrointestinal stromal tumours and "all rhabdomyosarcoma[s] that were not alveolar or pleomorphic".

⁷ van der Graaf WT, Blay JY, Chawla SP *et al*. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet* 2012;379:1879-1886.

Important baseline features of patients and their tumours were described. In 80% of subjects, lung was a site of disease. Prior anti-cancer therapy was similar across arms. For example, doxorubicin had been used by 98% in each arm, ifosfamide by 67-76%, docetaxel by 28% and gemcitabine by 34%. Frequencies of prior surgery and radiotherapy were also similar across arms.

Progression-free survival. This was the primary endpoint. Results are summarised in Table 7.

Table 7. Primary endpoint: PFS. Independent radiologist-assessed PFS (VEG110727; ITT population).

	Placebo (N=123)	Pazopanib (N=246)
Subject Classification, n (%)		
Progressed or died (event) ^a	106 (86)	163 (66)
Censored, follow-up ended ^b	16 (13)	73 (30)
Censored, follow-up ongoing ^c	1 (1)	10 (4)
Kaplan-Meier Estimate for PFS (weeks)^d		
1st quartile (95% CI)	3.9 (3.6, 4.1)	8.3 (8.1, 11.4)
Median (95% CI)	7.0 (4.4, 8.1)	20.0 (17.9, 21.3)
3rd quartile (95% CI)	11.4 (8.9, 12.1)	35.6 (28.1, 38.1)
Adjusted hazard ratio^e (95% CI)	0.35 (0.26, 0.48)	
Stratified log-rank p-value^e	<0.001	

Data Source: VEG110727 Table 7.1000

PFS: progression-free survival

- Includes 6 subjects in the placebo and 15 subjects in the pazopanib arm who died during adequate follow-up without documentation of progression (Data Source: VEG110727 Table 7.9300).
- Subjects were classified as censored with follow-up ended if any of the following occurred: (i) if the investigator determined that progression had occurred, but the independent radiologist did not have the same assessment, follow-up for progression would have stopped, leading to censoring with follow-up ended only for the independent review, (ii) the progression event occurred after a period of extended inadequate assessment (8 weeks [56 days] for visits occurring on or prior to the Week 12 visit and 12 weeks [84 days] for visits occurring post the Week 12 visit), (iii) subject started a new anti-cancer treatment prior to radiologically documented progression or (iv) subject withdrew from the study prior to disease progression (e.g., because of premature withdrawal from the study, [lost-to-follow-up]).
- Subjects were classified as censored with follow-up ongoing if they were still on-study and progression-free at their last disease assessment.
- Confidence intervals for quartiles are estimated using the Brookmeyer-Crowley method.
- Hazard ratios are estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log rank test are adjusted for WHO PS and number of prior lines of systemic treatment for advanced disease.

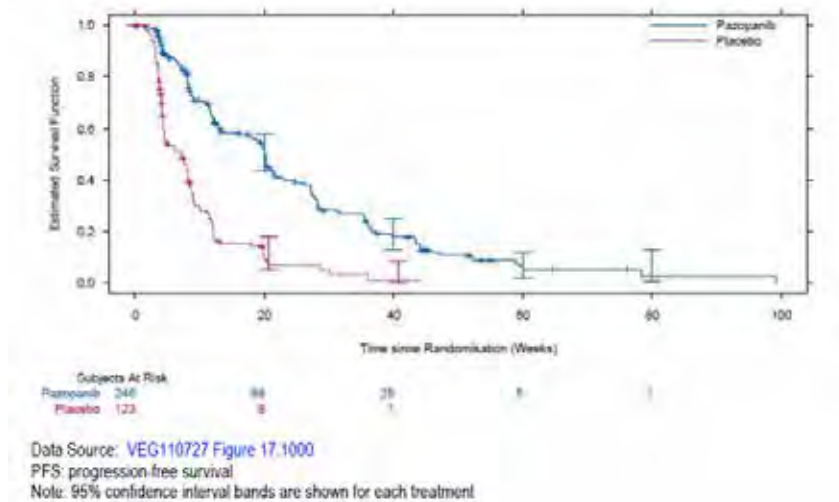
In the ITT population, assessed by independent radiologic review, median PFS in the placebo arm was 7.0 weeks (95% confidence interval (CI) 4.4-8.1) (1.6 months) and in the pazopanib arm 20.0 weeks (95% CI 17.9-21.3) (4.6 months). The hazard ratio (HR) was 0.35 (95% CI 0.26-0.48). Sensitivity analyses supported this finding.

A secondary aim was to examine PFS in three histology subtypes: leiomyosarcoma, synovial sarcoma and "other STS eligible histologies". HRs remained similar to that calculated for the primary endpoint, and even for synovial sarcoma with relatively few subjects, the HR was 0.43 (95% CI 0.19-0.98) in favour of pazopanib. Other subgroup analyses based on number of prior lines of systemic therapy, World Health Organization performance status, site of enrolment, tumour Grade, patient age, gender and race showed similar results.

Best overall response. Partial response was obtained by only 4% of pazopanib patients (according to independent radiology assessment) or 9% (according to investigator assessment), with no partial response in the placebo arm.

Overall survival. As of the clinical cut-off, 78 placebo subjects (63%) and 134 pazopanib subjects (56%) had died. Median OS in a pre-specified interim analysis was 10.4 months in the placebo arm and 11.9 months in the pazopanib arm (HR 0.82; 97.87% CI 0.59-1.14). The lack of a clear difference may be due to more use of anti-cancer therapy in the placebo arm following discontinuation of study drug (72% versus 54%); there was no cross-over to pazopanib; however, Kaplan-Meier OS curves were close even on therapy (Figure 1).

Figure 1. Kaplan-Meier graphs of PFS per independent radiologist assessment (VEG110727; ITT population)



Follow-up was longer for those with radiological progression in the placebo arm (median 6.8 months) than for those in the pazopanib arm (median 4.4 months). The US labelling document includes updated OS results from the protocol-specified final analysis; results were similar (12.6 versus 10.7 months; HR 0.87 [95% CI 0.67-1.12]).

Quality of life. Overall QoL (measured to Week 12) was not better in the pazopanib arm, and some contributing measures – fatigue, dyspnoea, appetite loss, diarrhoea, nausea and vomiting – were distinctly worse. The sponsor argued that inclusion of data to only 12 weeks restricted interpretation. The suspicion of a negative impact on QoL impacts on the meaningfulness of the observed improvement in PFS with pazopanib.

Study VEG20002

VEG20002 was a Phase II, open-label, non-randomised study in subjects with relapsed or refractory STS for whom no standard therapy existed. An 800 mg once daily dose was used.

The study was designed with two stages of enrolment, to allow an initial assessment of response by tumour type (leiomyosarcomas; adipocytic tumours; synovial sarcomas; and others) before further enrolment. Only 2 of 17 subjects with adipocytic tumours had at least stable disease after 12 weeks, so this stratum was closed to further enrolment.

The 138 subjects in the ITT population included n = 41 with leiomyosarcoma, 19 with adipocytic sarcoma, 37 with synovial sarcoma and 41 with other STS. The median age across the ITT population was 51 years (range 18-79 years).

12-week Progression-free survival rate. Overall, 41% were progression-free at 12 weeks (41-49% for leiomyosarcoma, synovial and “other” sarcomas; 26% for adipocytic sarcomas). The majority of progression-free patients at week 12 had stable disease rather than partial remission (overall 37% and 4%, respectively).

Progression-free survival. Median PFS was 12.1 weeks (Table 8, below) medians were 17.2 weeks for leiomyosarcoma, 11.1 weeks for adipocytic sarcoma, 23.4 weeks for synovial sarcoma and 14.0 weeks for other STS.

Table 8. Summary of Kaplan-Meier estimates of PFS (VEG20002; ITT population).

Category ^a	Leiomyo- sarcoma N=41	Adipocytic sarcoma N=19	Synovial sarcoma N=37	Other STS N=41	Total N=138
Number of Subjects, n (%)					
Progressed or Died	29 (71)	14 (74)	25 (68)	25 (61)	93 (67)
Censored, follow-up ended	12 (29)	5 (26)	12 (32)	14 (34)	43 (31)
Censored, follow-up ongoing	0	0	0	2 (5)	2 (1)
Estimates for progression-free survival (weeks)^b					
1st quartile (90% CI)	11.2 (8.9, 12.0)	6.6 (3.9, 11.1)	10.0 (6.6, 11.9)	10.9 (8.3, 12.0)	10.4 (8.7, 11.3)
Median (90% CI)	17.2 (12.0, 24.1)	11.1 (7.1, 11.9)	23.4 (11.7, 29.3)	14.0 (12.0, 36.3)	12.1 (12.0, 22.4)
3rd quartile (90% CI)	34.6 (24.1, 36.7)	12.0 (11.1, 22.9)	41.0 (24.9, 49.0)	119.1 (24.1, -)	36.3 (24.9, 46.4)

Data Source: VEG20002 Table 7.2000

PFS: progression free survival; STS: soft tissue sarcoma

a. This is investigator data.

b. Quartiles were estimated using the Brookmeyer-Crowley method.

Overall survival. Median OS was 10.6 months: 6.5 months for adipocytic sarcoma and 9.8-11.7 months for others (Table 9).

Table 9. Summary of Kaplan-Meier estimates of OS (VEG20002; ITT population).

Category	Leiomyo- sarcoma N=41	Adipocytic sarcoma N=19	Synovial sarcoma N=37	Other STS N=41	Total N=138
Number of Subjects, n (%)					
Died	36 (88)	17 (89)	33 (89)	38 (93)	124 (90)
Censored, follow-up ended	2 (5)	2 (11)	1 (3)	0	5 (4)
Censored, follow-up ongoing	3 (7)	0	3 (8)	3 (7)	9 (7)
Estimates for overall survival (months)^a					
1st quartile (90% CI)	8.0 (5.2, 10.6)	3.5 (2.5, 5.3)	5.0 (3.0, 9.3)	6.6 (5.0, 7.6)	5.8.0 (4.8, 6.9)
Median (90% CI)	11.7 (10.6, 17.6)	6.5 (4.2, 19.3)	10.3 (7.6, 13.2)	9.8 (7.6, 11.3)	10.6 (9.5, 11.7)
3rd quartile (90% CI)	19.6 (17.4, 37.6)	20.1 11.2, 27.4	16.8 13.2, 28.5	24.7 (11.3, 33.7)	22.1 (17.6, 24.7)

Data Source: VEG20002 Table 7.3010

OS: Overall survival; STS: soft tissue sarcoma

a. Quartiles were estimated using the Brookmeyer-Crowley method.

PFS in leiomyosarcoma and synovial sarcoma patients was consistent across studies, as shown in Table 10:

Table 10. Median PFS in pazopanib recipients.

Median PFS (months) in pazopanib recipients		
Tumour class (detail differs across studies)	Pivotal (VEG110727)	Supportive (VEG20002)
Leiomyosarcoma	20.1	17.2
Synovial sarcoma	17.9	23.4
Adipocytic sarcoma	-	11.1
Other STS	20.1	14.0

Safety

Exposure

In VEG110727 and VEG20002, a total of 382 subjects received pazopanib for treatment of STS. Median duration of exposure in this pooled population was 3.6 months, with 42/382 subjects (11%) receiving treatment for a period > 12 months. In VEG110727, median duration was 8.1 weeks for placebo and 16.4 weeks for pazopanib (see Table 11).

Table 11. Overview of safety

Adverse Events	VEG110727	VEG110727	VEG20002
	Placebo (n=123)	Pazopanib (n=240)	(n=142)
Grade 3-4	30 (25%)	141 (59%)	48%
Serious	29 (24%)	99 (41%)	29%
Treatment-related Serious	6 (5%)	57 (24%)	18%
Discontinuation due to AEs	6 (5%)	48 (20%)	NA (>7%)

Fatal serious AEs were reported in 5% of placebo subjects and 3% of pazopanib subjects in VEG110727.

In VEG110727, in the pazopanib arm, permanent discontinuation due to AEs was seen in 48/240 (20%) – a high proportion – versus 6/123 (5%) in the placebo arm. A range of AEs caused permanent discontinuation; the three most common AEs were alanine aminotransferase (ALT) increased, dyspnoea, and left ventricular dysfunction. Likewise, 32% of pazopanib subjects required dose reduction due to AEs (commonly, fatigue, hypertension, diarrhoea and nausea), and 50% required dose interruption.

In VEG110727, compared to the placebo arm, pazopanib treatment was associated with an increase in the incidence of every commonly encountered AE except constipation, and this exception is probably due to the diarrhoea-inducing toxicity of pazopanib.

Specific safety issues are outlined below.

Thromboembolism

In 2/8 pazopanib subjects (and 0/6 placebo subjects) who died of a serious AE in VEG110727, pulmonary embolism was reported but not considered treatment-related. Incidence rates across arms suggest a possible small increase in venous thromboembolism with pazopanib. Venous thromboembolic event rates in STS studies were higher than in RCC studies. Rates for arterial thromboembolism were similar to those seen in RCC studies.

Observational Study WEUSRTP4987 examined the incidence of thromboembolic events in STS patients. This study did not address the role of pazopanib in thromboembolism.

Cardiotoxicity

Left ventricular dysfunction was commonly reported (with 4/382 patients having severe dysfunction). It is unclear whether this was caused by, exacerbated by, or independent of hypertension. Cardiotoxicity is a risk with sunitinib (which also inhibits VEGFR and PDGFR). New text about LV dysfunction in STS subjects is proposed for the recently introduced PI *Precaution* regarding cardiac dysfunction.

Pneumothorax

An increase in pneumothorax frequency with pazopanib was postulated as due to necrosis of peripheral sarcoma lesions in the lung. The incidence in RCC studies was lower. Pneumothorax has been reported in case series of STS patients⁸.

Safety concerns also seen in RCC studies

Hepatotoxicity. Serious hepatotoxicity (using Hy's Law threshold⁹) was observed in 5/240 pazopanib subjects in VEG110727, and in 1/123 placebo subjects. There was one fatality in the pazopanib population (multi-organ failure associated with major hepatic dysfunction); the clinical evaluator mentions a possible other fatal case. There was a clear increase in frequency of ALT or aspartate aminotransferase (AST) elevations in the pazopanib arm of VEG110727. In two of four subjects re-challenged with pazopanib, liver function test (LFT) abnormalities recurred.

There is a coherent picture of pazopanib-induced hepatocellular injury, sometimes serious. Most significant transaminase elevations occurred in the first 18 weeks of treatment (median duration of exposure was less than this). There is a boxed warning regarding severe or fatal hepatotoxicity in the current PI.

Hypertension. This was a common AE, but no more so than in RCC studies; there was no report of hypertensive crisis in STS studies. Hypertension was a common cause of dose interruption or reduction and treatment cessation. The sponsor has proposed some useful changes to the PI *Precaution* regarding hypertension.

Bleeding. Haemorrhagic events were more common with pazopanib than placebo, although most events were not severe. Data were consistent with RCC study data.

Bowel perforation. Four pazopanib subjects reported bowel perforation or fistula; all 4/382 had known abdominal metastases and in 2/4, the perforation was shown to be at the site of metastasis; one of these cases was fatal. Location of disease in VEG110727 was 'abdominal cavity' in about 29% (66/246 pazopanib subjects).

Hypo- and hyper-thyroidism was encountered in RCC studies. Incidence of proteinuria was similar in STS and RCC studies; one case of nephrotic syndrome resulted in study discontinuation. Haematological abnormalities distinctly more prominent in the pazopanib arm than the placebo arm in VEG110727 were neutropenia (and leukopenia) and thrombocytopenia. Various biochemical abnormalities were seen more often in the pazopanib arm of VEG110727 than in the placebo arm. Weight decrease was a prominent finding (treatment related in 23% of pooled pazopanib STS patients), mirrored in nonclinical studies.

Comparison with safety in RCC

The clinical evaluator considered differences in the safety profile of pazopanib in STS compared to RCC to be minor, but noted a higher frequency of serious AEs in the STS studies than in the three pivotal RCC studies (37% versus 27%). The incidence of myocardial dysfunction was singled out as being higher in STS studies, possibly due to previous anthracycline exposure. Also, the increased incidence of pneumothorax was not seen in RCC studies.

⁸van der Graaf WT, Blay JY, Chawla SP *et al.* Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet* 2012;379:1879-1886.

⁹ Refer to the FDA document *Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, July 2009. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Paediatric use

It is estimated that in Australia there are approximately 800 new sarcoma cases each year, with only approximately 33 new cases in children 0-14 years old.

Studies in juvenile rats have generated an important safety signal regarding use of pazopanib in children. Pre-weanling rat studies showed “a profound adverse effect on the growth and development of the major organ systems... and associated deaths when treatment started soon after birth” possibly due to abnormal vessel development. In older juvenile rats, the toxicity profile was closer to that in adult rats. However, (a) deaths occurred in these ‘older juvenile’ rats; (b) toxicity was seen after a shorter duration of exposure than in adult rats; (c) toxicity was somewhat more severe in juvenile rats dosed beginning at day 21 post-partum than when dosed beginning at > 6-8 weeks of age, and (d) toxicity in some cases was irreversible.

The proposed STS indication does not include any restriction according to age. The sponsor considers that given the severity of metastatic cancer in children, and the limited treatment options, there should be “flexibility in the option to use pazopanib”.

The current pazopanib PI states in the *Dosage and Administration* section: ‘*The safety and efficacy of VOTRIENT in children have not been established.*’ In correspondence to the TGA, the sponsor proposed to change this to: ‘*VOTRIENT is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy (see Precautions).*’

The proposed PI includes a new *Precaution* regarding use in children. It states that Votrient should not be given to patients younger than 2 years of age. Juvenile rat studies suggest a gradient of toxicity, increasing with decreasing age. Clinical trials in STS were in adults.

A Phase I study of pazopanib as single-agent therapy for children with refractory solid tumours, ADVL0815, is being conducted in the US and Canada by the Children’s Oncology Group. The sponsor states in a letter dated 1st May 2012 that in this study, no adverse effects on bone growth or teeth have been seen. As of 1st January 2012, 53 patients were enrolled, with a total exposure of 195 cycles of 28 days (median 2 cycles per patient, range 1-20). The age range of children in the study was not stated.

Clinical evaluator’s recommendation

The clinical evaluator recommends approval of the proposed indication supported registration.

Risk management plan

The proposed RMP was found generally acceptable by the TGA’s OPR.

Risk-benefit analysis

Delegate considerations

Efficacy

The decision to study the heterogeneous “soft tissue sarcoma” group is pragmatic given the rarity of individual tumour types. Despite this, there is apparently reliable evidence from a well-conducted Phase III study of some efficacy in defined STS types, with supporting evidence from a Phase II study. In placebo-controlled VEG110727, the duration of PFS was extended in the pazopanib arm. This result was accompanied by neither

statistically significant improvement in OS nor by improvement in QoL, but extension of PFS may for some patients be meaningful in its own right.

Safety

Pazopanib is associated with multiple significant toxic side-effects, most prominently hepatotoxicity. STS studies revealed signals regarding thromboembolism, cardiotoxicity and pneumothorax. Other AEs encountered in STS studies were broadly consistent with the safety profile seen in RCC studies, although it was noted that serious AEs were more commonly encountered in STS studies than in RCC studies.

There was some indication that pazopanib exposure was higher in STS than in RCC patients (see *Pharmacokinetics*, above), however this did not stop selection of 800 mg daily as the STS Phase III study dose. Another explanation for the difference in serious AE frequency is the difference in RCC and STS patient populations.

VEG110727 had significant exclusion criteria, so some safety outcomes may represent a “best case” scenario. The real-world AE profile may be worse, despite PI statements aimed at mitigating risk.

An important safety consideration is the lack of paediatric safety (and efficacy) data, given a strong signal of toxicity in pre-weanling rats.

Bowel perforation may be predicted in patients with known bowel metastases. The Delegate considered it sensible to contra-indicate use in patients with known bowel wall involvement.

Indications and risk-benefit balance

The proposed extension of indication is to include *‘treatment of patients with advanced (unresectable and/or metastatic) Soft Tissue Sarcoma (STS) who have received prior anthracycline treatment or for patients who are unsuited for such therapy. There is a caveat as part of the proposed indication, as follows: ‘The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma.’*

Efficacy across STS subtypes. The lower efficacy against adipocytic sarcomas in VEG20002 and the exclusion of this histological type in VEG110727 are reflected in the caveat above. The EU indication¹⁰ may be more stringent with regard to details of STS studied (and not studied) in VEG110727. The draft Australian PI notes only that adipocytic STS and GIST were not studied. Exclusion of STS subtypes should be better explained in the approved PI *Clinical Trials* section, but otherwise in this regard, the proposed indication is reasonable.

Locally advanced, unresectable disease. The proposed indication allows use in advanced (unresectable) disease with no metastases. A clear inclusion criterion in VEG110727 was “metastatic disease and not only locally advanced disease”. This is taken to mean that disease progression on prior therapy could have been progression from locally advanced to metastatic disease, or progression of metastatic disease. Only one subject in VEG110727 was specified as having the protocol deviation of “locally advanced disease only”. This is taken to mean that the inclusion criterion was generally followed. Use in unresectable local disease appears to fall outside of the scope of the pivotal study. However, this aspect of the indication’s wording (“unresectable and/or metastatic”) may be reasonable given the poor prognosis of patients with locally unresectable disease – assuming such disease is neither low grade nor has special features making no or very slow progression likely.

¹⁰ The EMA website (checked 26-6-2012) states that the CHMP adopted the following STS indication: *Votrient is indicated for the treatment of adult patients with selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Efficacy and safety have only been established in certain STS histological tumour subtypes (see section 5.1).* The relevant update to Section 5.1 (Clinical Trials) was not available at time of checking.

Patients unsuited to anthracyclines. The indication allows use in patients “unsuited to” anthracycline therapy. Anthracyclines are associated with serious irreversible myocardial toxicity (with delayed congestive cardiac failure), and with severe myelosuppression. Contraindications for Adriamycin (doxorubicin) are as follows:

Adriamycin therapy should not be started in patients who have marked myelosuppression or severe stomatitis induced by previous treatment with other antitumour agents or by radiotherapy. Situations in which patients should not be treated with i.v. Adriamycin include patients with severe arrhythmias, myocardial insufficiency, myocardial infarction. Adriamycin treatment is contraindicated in patients who have previously received treatment with full cumulative doses of Adriamycin and Daunorubicin.

Adriamycin therapy is also contraindicated in patients with marked liver impairment, in pregnancy and lactation (see Precautions), in the presence of generalised infection, and in patients with hypersensitivity to Adriamycin and/or other anthracyclines or anthracenediones.

Similar contraindications exist for epirubicin. Formal contraindications for liposomal doxorubicin are less stringent, but liposomal doxorubicin has no formal indication in STS.

It is possible that by accepting the pazopanib STS indication as currently worded, pazopanib will be used in subjects with contraindications for doxorubicin/epirubicin. Although VEG110727 included patients who had been intolerant to anthracycline-based regimens, this is not taken to mean patients with medical contraindications to the use of anthracycline based regimens. There is an overlap between anthracycline contraindications, VEG110727 exclusion criteria (regarding, for example, bone marrow or cardiac function) and some known adverse effects of pazopanib (for example, neutropenia, cardiotoxicity).

Alternative indication

The Delegate proposed the following alternative indication:

Treatment of patients with advanced (unresectable and/or metastatic) Soft Tissue Sarcoma (STS) who have received prior anthracycline treatment (including patients intolerant of such therapy).

The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma (see Clinical Trials).

The Delegate considered there is a positive risk-benefit balance for pazopanib in this revised indication.

Trabectedin

It is relevant that a previous application to register the new chemical entity, trabectedin for use in STS was withdrawn several years ago¹¹. The pivotal STS trial (in leiomyosarcoma or liposarcoma patients who had relapsed on or were refractory to anthracycline and ifosfamide; median age 53 years) had no (non-trabectedin) active comparator arm, but median PFS was up to 3.3 months and median OS was up to 13.8 months. About half of subjects received subsequent anti-cancer treatments. Median PFS was shorter in supportive STS trials. Toxicity was a key concern.

Ignoring for a moment the problems with cross-study comparison, it is worth noting that the median PFS for pazopanib was higher than for trabectedin (4.6 month versus 3.3 months), but OS was slightly lower (11.9 months versus 13.8 months). Overall survival in both studies was likely strongly influenced by available subsequent therapies.

¹¹ The AusPAR for trabectedin is available at <http://www.tga.gov.au/pdf/auspar/auspar-yondelis.pdf>

It is relevant in terms of the validity of results that, unlike the trabectedin STS submission, the current pazopanib application includes a Phase III, placebo-controlled study.

Proposed action

The Delegate proposed to approve the submission but vary the indication to state:

Treatment of patients with advanced (unresectable and / or metastatic) Soft Tissue Sarcoma (STS) who have received prior anthracycline treatment (including patients intolerant of such therapy).

The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma (see CLINICAL TRIALS).

The implementation of the RMP version most recently approved by the TGA's OPR was proposed as a condition of registration.

Advice requested from ACPM

The Delegate proposed to seek general advice on this application from the ACPM.

Response from sponsor

Purpose of application: To register a new indication to include treatment of patients with STS.

Based on the review of all submitted information the Delegate has recommended approval of Votrient treatment of patients with advanced STS (excluding specific sub types not studied in the pivotal trial). This recommendation is consistent with the approval in the US and a positive CHMP Opinion for a similar indication in the EU. A decision on a similar application is pending in Canada.

The company supports the Delegate's recommendation, which is supported by the submitted data which demonstrates the following:

- Efficacy is supported by a clinically and statistically significant improvement in PFS of a median 3 month benefit over placebo. Overall survival, which was the defined secondary outcome, showed an improvement in favour of pazopanib, although the result was not statistically significant.
- The safety profile is essentially similar to that observed for the approved RCC indication, with the exception of three new safety signals: myocardial dysfunction, venous thromboembolic events and pneumothorax identified in STS patients who may have been predisposed to these toxicities. These toxicities can be managed with appropriate monitoring and prompt intervention as recommended in the PI.
- The magnitude of benefit, coupled with the well characterised and manageable safety profile of pazopanib in patients with recurrent metastatic STS fulfils an unmet medical need. GSK and experts in STS believe that the benefit-risk assessment of pazopanib is favourable and represents a valuable treatment option for patients with this disease.

Response to points raised by Delegate for ACPM consideration

1. Indication

The Delegate has proposed the following revised indication:

"Votrient is indicated for the treatment of patients with advanced (unresectable and/or metastatic) Soft Tissue Sarcoma (STS) who have received prior anthracycline treatment (including patients intolerant of such therapy).

The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma.”

The sponsor requests that the indication be retained as proposed, with the following amendment:

“Votrient is indicated for the treatment of patients with advanced (unresectable and/or metastatic) Soft Tissue Sarcoma (STS) who have received prior chemotherapy or patients unsuited to such therapy.

The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma.”

This change from “prior anthracycline treatment” to “prior chemotherapy” is consistent with the indication approved in the US and the EU where prior anthracycline therapy is not mandated for the following reasons:

- Given the mechanism of action of a multi-kinase inhibitor such as pazopanib compared with chemotherapies, there is no scientific rationale to anticipate a difference in efficacy with pazopanib according to whether patient’s prior chemotherapy included anthracycline or not (that is, no cross resistance). This is supported by consistent demonstration of efficacy with pazopanib in patients who had received 0 or 1 lines of prior chemotherapy compared to those patients who had received 2+ lines of prior therapy.
- Anthracyclines carry a well known long term cardiotoxic risk, indeed some physicians already choose not to include them in first line regimens due to this safety issue. There is no reason to mandate that patients have to be exposed to anthracycline before treatment with pazopanib.
- *Albeit* comparing across studies, the efficacy data from the pazopanib Phase III study in a heavily pre-treated population appears at least commensurate with published data on doxorubicin in less heavily pre-treated STS patients. Therefore there are no data, nor a scientific rationale to suggest that it would be detrimental for patients to receive pazopanib monotherapy following non-anthracycline containing chemotherapy, should the physician/patient so choose.

Based on clinical rationale, GSK would like to maintain the text “or patients unsuited to such therapy” in the indication for the following reasons:

Two groups of patients are unsuited for prior chemotherapy in the metastatic setting:

1. those who have progressed within 12 months of neoadjuvant or adjuvant therapy and are therefore considered chemotherapy resistant, and
2. those who are too frail or have comorbidities that prohibit the use of chemotherapies.

The 27 patients (6% in the pazopanib group and 11% in the placebo group) in VEG110727 who were unsuited for prior chemotherapy are in the first group. Twenty two patients developed metastatic disease within 6 months of completing neoadjuvant or adjuvant chemotherapy and 5 recurred within 6-12 months of completing neoadjuvant or adjuvant therapy. These patients were unsuited for prior chemotherapy for metastatic disease because they had recurred soon after receiving neoadjuvant or adjuvant therapy and were therefore considered to be chemotherapy resistant. Treating such patients with additional chemotherapy would result in toxicity with little potential for benefit. These patients received significant benefit from pazopanib, however, with a HR of 0.25 (95% CI: 0.10, 0.65, $p < 0.001$) and medians of 8.9 (95% CI: 4.1, 10.1) and 28.1 (95% CI: 20.1, 35.4) weeks for the placebo and pazopanib groups, respectively, as shown in Table 12.

Table 12. Summary of statistical analysis of independent radiologist-assessed PFS in those patients with 0 prior lines of systemic treatments for advanced disease.

	Placebo (N=13)	Pazopanib (N=14)
Number of Subjects		
Progressed or Died	13 (100%)	10 (71%)
Censored, Follow-up ended	0 (0%)	4 (29%)
Adjusted Hazard Ratio [1]		
Estimate (95%CI)	0.25 (0.10,0.65)	
Stratified Log-Rank P-value [1]	<0.001	
Quartile Estimates in Weeks [2]		
1 st Quartile (95% CI)	4.1 (2.6,8.9)	20.1 (7.9,28.1)
Median (95% CI)	8.9 (4.1,10.1)	28.1 (20.1,35.4)
3rd Quartile (95% CI)	10.1 (8.9,13.0)	35.4 (24.7,59.4)

[1] Hazard ratios are estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test are adjusted for WHO performance status.

[2] Confidence intervals for quartiles are estimated using the Brookmeyer-Crowley method.

The second group of patients unsuited for prior chemotherapy for metastatic disease (those who are too frail or have comorbidities that prohibit the use of chemotherapies) have no other proven treatment options. The differential safety profile of pazopanib compared with chemotherapy indicates that pazopanib may provide a tolerable therapy for these patients. Therefore, although this group of patients was not specifically studied in VEG110727, they should be included in the indication statement to provide pazopanib as a treatment option.

In conclusion, the retention of the statement “or patients unsuited to such therapy” is justified on the basis that there are some patients with metastatic STS who would not be considered by their physicians as appropriate to receive anthracyclines or other chemotherapies due to their toxicities. The proposed indication does not preclude those patients who have not received anthracyclines from treatment with pazopanib.

2. Efficacy outcomes

Soft tissue sarcomas are rare and orphan diseases which account for less than 1% of all cancers. Approximately 50% of patients with STS develop metastatic disease. Recurrent metastatic disease is characterised by bulky tumors that involve multiple organs and impinge on vital structures. Rapid progression of the disease leads to increased morbidity. Patients with metastatic STS are treated with sequential chemotherapies. The use of these chemotherapies is based largely on limited data from single arm or randomised Phase II studies. Despite these therapies, progressive disease is inevitable and constitutes an area of unmet medical need for new and effective therapies that could benefit these patients.

To meet this need, the efficacy and safety of pazopanib was investigated in a well conducted, randomised, double-blind, placebo controlled Phase III trial in patients with bulky metastatic STS who had progressed on or after prior chemotherapy. This is the first Phase III trial to be conducted in heavily pre-treated patients with recurrent, metastatic STS. It was designed in collaboration with the EORTC-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG), a premier academic group of sarcoma investigators. This trial

demonstrated a clinically and statistically significant improvement in PFS with pazopanib compared to placebo.

Sarcoma experts consider the 3 month median benefit in PFS in the pazopanib versus placebo group as clinically compelling, especially in a patient population with bulky and rapidly progressive disease; the latter being evidenced in the placebo arm with a median PFS time of only 7 weeks. Importantly, the PFS benefit with pazopanib was observed irrespective of the extent of prior chemotherapy treatment. The secondary outcome, OS, favoured pazopanib, although it was not statistically significant. The robust treatment effect for PFS, the primary endpoint of this study, and the directional difference observed for OS support the benefit of pazopanib over placebo in this patient population.

The Phase III trial also demonstrated that there was a decline from baseline in the Global Health Status/QOL summary scale in each of the treatment arms. Although numerically favouring the placebo arm, and as measured by the minimally important clinical difference (MICD), there were no clinically or statistically significant differences between the pazopanib and placebo addition to the small number of assessments. A limitation of the health outcomes assessments is the considerable dropout of subjects due to disease progression, particularly in the placebo arm (median PFS 7.0 weeks). This could bias results in favour of the placebo arm as subjects who drop out would be expected to have a worse mean change from baseline score than subjects who remained on study. Additionally no health outcome assessments were performed after disease progression to document the potential negative impact of progression upon the Global Health Status/QoL summary scale.

3. Safety profile of votrient in STS patients

Comparative safety profile to RCC patients

The overall safety profile of pazopanib in STS is similar to the established profile (as outlined in the Votrient PI) for RCC. The previously identified safety signals in the RCC study populations, including hepatotoxicity, hypertension, diarrhoea, arterial thromboembolic events, hemorrhagic events, thyroid function abnormalities, bowel perforations and fistulae, were observed in the STS population. Three new safety signals: myocardial dysfunction, venous thromboembolic events and pneumothorax, were identified in STS patients who may have been predisposed to these toxicities. These toxicities can be managed with appropriate monitoring and prompt intervention, as discussed below.

• Myocardial dysfunction

- The clinical and subclinical cardiotoxicity associated with anthracyclines is well recognised. As a result, LVEF monitoring at baseline and every 12 weeks was instituted in VEG110727. Myocardial dysfunction was predominantly due to asymptomatic LVEF decline and this is in keeping with the literature on VEGF TKIs¹². None of the events were fatal. Although a direct cardiotoxic affect cannot be excluded, nonclinical studies did not reveal any direct cardiotoxicity from pazopanib. Hypertension and the resultant increased cardiac afterload may exacerbate LVEF in patients previously exposed to anthracyclines. This hypothesis is supported by the fact that the majority of patients with documented LVEF decline had hypertension and/or the requirement of new anti-hypertensive medication. Patients who continued on pazopanib were able to be managed by either pazopanib dose interruption or reduction and control of hypertension. Therefore, monitoring of LVEF, along with rigorous control of blood pressure and modification of pazopanib dosing are recommended in the proposed labelling

¹² Vaklavas C, Lenihan D *et al.* Anti-Vascular Endothelial Growth Factor Therapies and Cardiovascular Toxicity: What Are the Important Clinical Markers to Target? *The Oncologist* 2010;15:130–141.

guidelines (*Precautions* section) for patients at risk of myocardial dysfunction (for example, those with prior therapy with anthracyclines).

- **Venous thromboembolic events**

- Venous thromboembolic events occurred at a higher rate in the pazopanib arm compared with placebo. The exposure adjusted rate of venous thromboembolic events in the pazopanib and placebo arms were similar, indicating that the higher number of events in the pazopanib arm may be explained by the longer treatment period compared to patients in the placebo arm. Two patients on pazopanib experienced fatal venous thromboembolic events which were confounded by co-existing medical conditions including progressive disease. Venous thromboembolic event is a recognised complication of malignancy, although reported rates of venous thromboembolic events vary markedly. Despite this an increased rate of venous thromboembolic events with pazopanib in STS cannot be completely ruled out and is, therefore, addressed in the proposed PI (*Precautions* section).

- **Pneumothorax**

- Pneumothorax is a recognised complication in patients with sarcoma. The majority of cases reported were low grade. In addition to the increased risk of spontaneous pneumothorax with sarcomas, pooled data from one study showed that one-half of patients with sarcoma received doxorubicin-based chemotherapy prior to their pneumothorax. Necrosis of peripherally located pulmonary or pleural lesions in response to active therapy is postulated to be responsible for pneumothorax development. Pneumothorax is addressed in the proposed PI (*Adverse Reactions* section) for this indication.

PK exposure in RCC versus STS patients

The identical sparse blood sampling scheme was used in the Phase II study of pazopanib in subjects with RCC (VEG102616) and the Phase II study of pazopanib in subjects with STS (VEG20002). The mean plasma pazopanib concentrations from Study VEG20002 in subjects with STS were greater than the mean values from Study VEG102616 in subjects with RCC at all time points at which a blood sample was obtained. The differences between the mean plasma pazopanib concentrations in subjects with STS and subjects with RCC ranged from approximately 8% to 29%. Importantly, only 4 of the 295 individual concentrations in subjects with STS on Day 29 (1 at the 3-4 h time point and 3 at the 24 h post-dose timepoint) were greater than the range of values seen at the same points in subjects with RCC. Therefore, these results suggest that there was no marked difference in pazopanib PK between subjects with STS and subjects with RCC and, as such, no difference in safety risks due to increased exposure in the STS population.

Recommendation to include a contraindication for patient with known malignant disease involving the bowel wall.

Abdominal involvement in metastatic RCC and metastatic STS is common. The data generated in the Phase III trials for both RCC and STS (in patients with advanced metastatic disease) indicate that bowel perforations are uncommon (0.9% in RCC and 1% in STS).

GSK considers the current precaution on “Gastrointestinal Perforations and Fistula”, which was approved by the TGA for the RCC indication without a requirement for a contraindication, is also appropriate for the STS indication given the similar incidence of bowel perforations in both the RCC and STS trials. This position is also consistent with the labelling in the EU, US and other international markets in which this product is currently registered.

The use of pazopanib in RCC patients with known malignant disease involving the bowel wall is currently permitted with appropriate precautions. A contraindication in this patient population, in whom the product is currently approved for use would only be warranted if there were new data to suggest a significant change in the incidence of bowel perforations compared with the clinical trial data on which the current label was approved, which is not the case.

Finally, contraindicating this patient population would preclude access to Votrient even if a positive benefit risk was determined. Therefore, this is more appropriately managed as a precaution to allow for clinical judgement so that risk-benefit can be assessed on a case by case basis.

4. Conclusion and positive risk benefit assessment

Soft tissue sarcomas are rare and orphan diseases which accounts for less than 1% of all cancers. Approximately 50% of patients with STS develop metastatic disease. Recurrent metastatic disease is characterised by bulky tumours that involve multiple organs and impinge on vital structures. Rapid progression of the disease leads to increased morbidity. Patients with metastatic STS are treated with sequential chemotherapies. The use of these chemotherapies is based largely on limited data from single arm or randomised Phase II studies. Despite these therapies, progressive disease is inevitable and constitutes an area of unmet medical need for new and effective therapies that could benefit these patients.

To address this unmet need, the efficacy and safety of pazopanib was investigated in a well conducted, randomised, double-blind, placebo controlled Phase III trial in patients with bulky metastatic STS who had progressed on or after prior chemotherapy. This is the first Phase III trial to be conducted in heavily pre-treated patients with recurrent, metastatic STS. It was designed in collaboration with the EORTC-SBSTG, a premier academic group of sarcoma investigators, and US sarcoma experts. This trial demonstrated a clinically and statistically significant improvement in PFS with pazopanib compared to placebo. Sarcoma experts consider the 3 month median benefit in PFS as clinically compelling, especially in a patient population with bulky and rapidly progressive disease; the latter being evidenced in the placebo arm. Importantly, the PFS benefit with pazopanib was observed irrespective of the extent of prior chemotherapy treatment. The OS result favoured pazopanib, although it was not statistically significant. The actual power of the study to detect a 3 month benefit in OS with pazopanib (commensurate with the PFS benefit observed in this trial) was less than 50%. A trial adequately powered to detect a 3 month OS benefit would require a sample size in excess of 750 patients, which would be impractical for the specific subtypes of STS included in VEG110727.

The benefits observed must be weighed against pazopanib-induced risks. The risks associated with pazopanib have been well characterised through a large clinical development program and through post-marketing experience with RCC. The safety profile of pazopanib in STS patients is generally consistent with the Votrient PI for RCC. Three new safety signals: myocardial dysfunction, venous thromboembolic events and pneumothorax, were identified. STS patients may be predisposed to these toxicities. Myocardial dysfunction in these patients, all exposed to prior anthracycline, was predominantly due to asymptomatic decline in LVEF. Symptomatic LVEF decline was generally reversible if managed appropriately, as evidenced in the pivotal study. With baseline and periodic LVEF monitoring, and prompt and effective management of hypertension, this toxicity can be mitigated. Venous thromboembolic events are a well known complication of cancer, and the exposure adjusted rates are higher in STS compared with RCC, irrespective of treatment. Although a causal relationship between venous thromboembolic events and pazopanib is questionable, guidance for this AE has been included in the proposed PI. Pneumothorax is a recognised but rare complication of STS which may occur spontaneously or following active therapy. Awareness of this rare

complication would allow patients and healthcare providers to detect this complication and intervene appropriately.

Comparing across studies, the efficacy and safety profile of pazopanib in heavily pre-treated patients appears favourable when compared with published data on chemotherapies in either treatment naïve or less heavily pre-treated patients with STS.

The magnitude of benefit, coupled with the well characterised and generally manageable safety profile of pazopanib in patients with recurrent metastatic STS fulfils an unmet medical need. GSK and experts in STS believe that the benefit-risk of pazopanib is favourable and represents a valuable treatment option for patients with this disease.

Product Information: Amendments

A revised PI is provided. Details of revisions are beyond the scope of this AusPAR.

Risk management plan

A revised RMP is now available, incorporating changes recommended during the EU and TGA evaluations. An Australian specific annex is included.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall positive benefit-risk profile for the indication.

For the treatment of advanced (unresectable and/or metastatic) soft tissue sarcoma (STS) in patients who, unless otherwise contraindicated, have received prior chemotherapy including an anthracycline treatment

In making this recommendation the ACPM noted the local site and central review processes, however expressed significant concern with the lack of independence in the review of histology grade and subtype, and absence of evidence that the distribution of tumours, determined by histologic subtype and Grade, is balanced between the randomised groups. The ACPM expressed concern about the discrepancy in the partial response analysis between the independent radiology review and GSK sponsored investigator assessment using the objective RECIST criteria.

The ACPM agreed with the Delegate to the proposed amendments to the PI and Consumer Medicine Information (CMI) and advised that:

- a statement is in the *Clinical Trials* section of the PI to inform prescribers that the Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma.

The ACPM agreed with the Delegate on the proposed conditions of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Votrient tablets, containing pazopanib 200 and 400 mg, for the following indication:

For the treatment of 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.

The full indications are now:

VOTRIENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC).

VOTRIENT is indicated for the 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.

Specific conditions of registration applying to these goods

The implementation in Australia of the pazopanib RMP, dated 1 February 2011, and any subsequent revisions, as agreed with the TGA and its OPR.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report.

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Reference/Publication #