pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Pazopanib (Votrient) **Submitter's Funding Request:** Adult patients with selective subtypes of advanced Soft Tissue Sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Funding is not requested for patients with GIST and adipocytic soft tissue sarcomas.	
Submitted By: GlaxoSmithKline Inc.	**Manufactured By:** GlaxoSmithKline Inc
NOC Date: July 12, 2012	**Submission Date:** June 4, 2012
Initial Recommendation: October 4, 2012	**Final Recommendation:** November 29, 2012

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding pazopanib (Votrient) for patients with soft tissue sarcoma. The Committee acknowledged the need for more effective treatments for patients with STS, however, it made this recommendation because, as compared with placebo, pazopanib conferred only a modest progression-free survival benefit, no overall survival benefit, no measured improvement in quality of life and was not shown to be cost-effective.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps for stakeholders were identified by pERC.

SUMMARY OF pERC DELIBERATIONS

pERC noted that there are currently few treatment options for soft tissue sarcoma (STS) and that these treatments have not been well evaluated in the past for their clinical efficacy. There is a need for more effective treatments with less toxicity to improve quality of life and extend overall survival. Current treatments for patients with STS include doxorubicin-based chemotherapy regimens and ifosfamide. The pCODR systematic review included one randomized controlled trial comparing pazopanib with placebo in patients who had received prior systemic therapies or who were not suited for such therapies (PALETTE, van der Graaf et al 2012). Patients diagnosed with gastrointestinal stromal tumours (GIST) or adipocytic sarcoma were excluded from this study.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results from the PALETTE study in the context of patient values. Overall survival and quality of life improvements were not observed, although pazopanib, as compared with placebo, provides some clinical benefit for patients in terms of delaying progression. pERC discussed that the magnitude of the absolute benefit in progression-free survival was modest for pazopanib compared with placebo (median 4.6 months versus 1.6 months, respectively). pERC noted that the difference in measured overall survival between pazopanib and placebo was small and not statistically significant. pERC also considered that global quality of life measures were similar between pazopanib and placebo at 12 weeks. pERC further discussed the uncertainty associated with these quality of life results because of the large proportion of patients who had dropped out of PALETTE prior to its measurement at 12 weeks, particularly in the placebo group, which may have biased the results. pERC also discussed the side effect profile of pazopanib based on the results of PALETTE and in the context of side effects with other treatments commonly used for patients with STS. It was noted that there may be serious adverse events with all these options, however, pERC considered it challenging to interpret the toxicity profile of pazopanib as it was compared with placebo and not with therapies that may be used in clinical practice.

pERC reconsidered its Initial Recommendation based on feedback from the manufacturer concerning the results of the PALETTE study. While the Committee acknowledged there is a clinical effect of pazopanib, given the modest benefits observed, the absence of a survival benefit or robust quality of life data, and the potential for toxicities, pERC reiterated that it could not conclude that there was an overall net clinical benefit. pERC expressed interest in obtaining more quality of life data but it was noted that the manufacturer had indicated there was no additional quality of life information publicly available on pazopanib for patients with STS.

pERC also deliberated on input provided by a patient advocacy group indicating patients value treatments that will extend life, improve quality of life and have less toxicity compared with current therapies. pERC noted that an overall survival benefit was not observed in PALETTE and that the toxicity of pazopanib relative to the currently available treatments is unclear since it was compared with placebo. pERC noted the challenges with the quality of life data from the PALETTE study, however, pERC also considered that pazopanib is an oral therapy, which could improve some aspects of quality of life compared with intravenous therapies commonly used in the treatment of soft tissue sarcoma. Therefore, overall, pERC considered that pazopanib partially aligned with patient values. Upon reconsideration of the pERC Initial Recommendation, the Committee acknowledged that oral therapies may be more convenient for patients, which could positively impact their quality of life. However, in the absence of robust quality of life data and because pazopanib was not compared with intravenous treatments in the PALETTE study, no firm conclusions could be made in this instance.

pERC discussed the cost-effectiveness of pazopanib and noted that the high quality of the manufacturer's submitted economic evaluation allowed the pCODR Economic Guidance Panel to have some certainty in the range of estimates provided. However, pERC concluded that pazopanib was not cost-effective based on the range of estimates provided.

pERC also considered the feasibility of implementing a funding recommendation for pazopanib and did not identify any key barriers to implementation. It was noted that pazopanib is a newly available treatment for a relatively small patient population, which could facilitate implementation.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group (Sarcoma Cancer Foundation of Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group
- the Submitter (GlaxoSmithKline Inc.)

The pERC Initial Recommendation was to not fund pazopanib (Votrient) in patients with soft tissue sarcoma.

Feedback on the pERC Initial Recommendation indicated that the manufacturer disagreed with the initial recommendation and pCODR's Provincial Advisory Group agreed in part with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of pazopanib on patient outcomes compared to standard therapies or placebo in the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior systemic therapies or who are unsuited for such therapies.

Studies included

The pCODR systematic review included one international, multicentre, double-blind randomized controlled trial (PALETTE) that compared the efficacy and safety of pazopanib to placebo. Patients received either 800 mg pazopanib once daily or matching placebo tablets until disease progression or unacceptable toxicity. Cross-over from placebo to pazopanib was not allowed. Accompanying medications and other supportive care were not reported for the PALETTE study.

Patient populations: Previously treated patients with performance status 0 or 1

PALETTE included patients aged ≥18 years with advanced soft tissue sarcoma and a WHO performance status of 0 or 1. All patients had received prior chemotherapy, 93% for advanced disease and 25% as (neo) adjuvant therapy. This included anthracyclines in 99% of patients (given for advanced disease in 82%) and 71% of patients had been treated with ifosfamide or analogues. Patients diagnosed with gastrointestinal stromal tumour or adipocytic sarcoma were excluded from this study.

Key efficacy results: No overall survival benefit and modest PFS benefit

Key efficacy outcomes deliberated upon by pERC included progression-free survival, the primary endpoint in PALETTE, and overall survival. Pazopanib was associated with an approximately three month improvement in progression-free survival compared to placebo (4.6 months versus 1.6 months, respectively; HR = 0.31, 95% CI: 0.24 to 0.40, P < 0.0001). Overall survival was not statistically significantly different between pazopanib and placebo. pERC considered that the progression-free survival benefit observed was modest and that an improvement in overall survival would be important for this patient population. Upon reconsideration of the pERC Initial Recommendation and based on feedback from the manufacturer, pERC re-deliberated upon the results of the PALETTE study. While the Committee acknowledged there is a clinical effect of pazopanib, given the modest benefit observed in progression-free survival and the lack of an overall survival benefit, pERC reiterated that information on

additional outcomes such as quality of life and toxicity compared to commonly used IV treatments would be very important.

Quality of life: Global quality of life similar but estimates may be biased

Quality of life was assessed in the first 12 weeks after randomization using the EORTC global quality of life scale as well as the health utility scale (EQ5D) in the PALETTE study. By week 12, more patients in the placebo group had dropped out of the study compared with the pazopanib group (74% versus 48%, respectively), which may have biased the results. Therefore, although global quality of life scores were similar between pazopanib and placebo, pERC considered that these data should be interpreted with caution. Upon reconsideration of the pERC Initial Recommendation, the Committee emphasized the importance of robust quality of life data to their deliberations, given the modest clinical effect of pazopanib on progression free survival. The Committee indicated it would have been interested in additional quality of life data. It was noted that the manufacturer had indicated there was currently no additional quality of life information available in the public domain on pazopanib in patients with STS.

Safety: Toxicity compared with current therapies used in STS unclear

More patients in the pazopanib arm experienced serious adverse events than the placebo arm (41% versus 24%, respectively). Grade 3 adverse events were reported for fatigue, diarrhoea, hypertension and anorexia. Grade 4 adverse events were rare, with one case of fatigue being reported in each group. pERC discussed that it was challenging to interpret the side effect profile of pazopanib as compared with placebo but that no unexpected adverse events were observed for pazopanib. pERC also discussed the side effect profile of other treatments commonly used for patients with STS. It was noted that there may be serious adverse events with all treatment options, including pazopanib, but that the relative toxicity of pazopanib compared with these treatments is uncertain given the placebo comparison made in the PALETTE study.

Need: Current therapies are IV, have limited effectiveness and substantial toxicities

Therapeutic options are limited for patients with soft tissue sarcoma. Standard chemotherapy agents, such as doxorubicin and ifosfamide, have limited effectiveness and toxicities may be substantial. Administration requires intravenous treatments every three to four weeks, which may be given as multi-day infusions to reduce toxicity. pERC acknowledged the need for new treatments in patients with advanced soft tissue sarcoma and noted that pazopanib is an oral agent but that, based on evidence from the PALETTE study, it may not address other needs (e.g., extending life and maintaining quality of life).

PATIENT-BASED VALUES

Values of patients with STS: Extending life and maintaining quality of life

pERC considered patient advocacy group input highlighting that extending life and maintaining quality of life are important values for patients with STS. The ability to lead a productive life while living with STS is important to patients. pERC noted that an overall survival benefit was not observed in PALETTE and that there were challenges interpreting the quality of life data from the PALETTE study.

Patient values on treatment: improved side effect profile and accessible treatments valued

pERC discussed patient advocacy group input indicating that reducing adverse effects and having accessible treatments are important considerations for patients. From a patient perspective, currently available treatment options for soft tissue sarcoma are time consuming and often associated with significant adverse effects. Patients indicated that they are willing to try treatments associated with side effects if there is the potential to prolong life or to have a reduced side effect profile as compared to current treatments. Furthermore, patient input indicated that access to currently available treatments which are intravenously administered and can limit access to treatment for some patients who live in remote or smaller communities. pERC noted that the toxicity of pazopanib compared with current treatments is unclear since it has been compared with placebo.

pERC also considered that pazopanib is an oral therapy, which could improve some aspects of quality of life compared with intravenous therapies used in the treatment of soft tissue sarcoma and improve accessibility for some patients. Upon reconsideration of the pERC Initial Recommendation, pERC further discussed differences in oral and intravenously administered therapies used to treat STS. The Committee acknowledged that oral therapies are more convenient, which could positively impact quality of life.

However, in the absence of robust quality of life data and because pazopanib was not compared with intravenous treatments in the PALETTE study, no firm conclusions could be made in this instance.

ECONOMIC EVALUATION

Economic model submitted: Cost effectiveness and cost-utility, previously treated patients

The pCODR Economic Guidance Panel assessed an economic evaluation of the cost effectiveness and cost-utility of pazopanib in patients with advanced soft tissue sarcoma STS (excluding gastrointestinal stromal tumour, GIST, and adipocytic sarcoma) who had received prior chemotherapy or were unsuited for such therapy.

Basis of the economic model: Clinical and economic inputs

Costs included drug costs and healthcare costs associated with active treatment, disease progression, best supportive care, and the costs associated with management of serious adverse events.

Key clinical effects included progression-free survival and overall survival estimates from the PALETTE study (Van der Graaf et al., 2012). The biggest influence on QALYs was the estimate of survival following tumour progression and model's time horizon.

Drug costs: Lower price submitted to pCODR

At the list price, pazopanib costs $41 per 200 mg tablet. At the recommended dose of 800 mg per day, the average cost per day in a 28-day course of pazopanib is $164 and the average cost per 28-day course is $4,592. At the lower submission price, which the manufacturer did not consider confidential, pazopanib costs $37 per 200 mg tablet; and at the recommended dose of 800 mg per day, the average cost per day in a 28-day course of pazopanib is $148 and the average cost per 28-day course is $4,144.

Cost-effectiveness estimates: good quality modeling but not cost-effective

The pCODR Economic Guidance Panel's (EGP) best estimate of the incremental cost-effectiveness ratio is between $146,950/QALY and $167,782/QALY when pazopanib is compared to placebo and based on the submitted price of $37 per 200mg tablet. The EGP considered both a partitioned-survival analysis approach that the manufacturer used to model survival and progression independently, which implicitly assumed that a patient's risk of dying before tumour progression is similar to the patient's risk of dying after tumour progression, and a post-progression based survival analysis approach, which corrected for this assumption. pERC noted that the EGP identified limitations in both modelling approaches but that the EGP's best estimates were based on the post-progression survival analysis approach. In addition, the submitted analyses were based on a ten-year time horizon, which is much longer than the PALETTE trial and extrapolation of benefits from short-term data may have a pronounced effect on clinical effect estimates in the economic model. The EGP based their best estimates on a five-year time horizon, which was an alternate duration of clinical benefit suggested by the pCODR Sarcoma Clinical Guidance Panel. pERC discussed these estimates of the cost-effectiveness of pazopanib and noted that the high quality of the manufacturer's submitted economic evaluation allowed the pCODR Economic Guidance Panel to have some certainty in the range of estimates that they provided. However, pERC considered that at the range of estimates identified, pazopanib was not cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: small patient population and access to oral therapies

pERC discussed the feasibility of implementing a funding recommendation for pazopanib and noted that pCODR's Provincial Advisory Group did not identify any key barriers to implementation. It was noted that pazopanib is a newly available treatment for a relatively small patient population, which could facilitate implementation. pERC also noted that as an oral drug, pazopanib will be more convenient for most patients. However, accessibility to oral cancer drugs may vary across jurisdictions.

pCODR's Provincial Advisory Group identified the potential for indication creep with the use of pazopanib in additional subtypes of soft tissue sarcomas. pERC noted that pazopanib is not likely to be used in the

treatment of GIST as there are well-established treatment options available for this population but that this could occur in the treatment of adipocytic tumours. However, pERC also noted that because this population is excluded from PALETTE, there is no randomized controlled trial evidence of the effectiveness of pazopanib in this population, which would limit its use in this setting.

DRUG AND CONDITION INFORMATION

Drug Information	• Tyrosine kinase inhibitor • 200mg tablets reviewed by pCODR • 800 mg administered orally once daily
Cancer Treated	• Selective subtypes of soft tissue sarcoma in patients who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy
Burden of Illness	• Peak age incidence of STS is 60-80 years, but may occur in adolescents and young adults with incidence rates ranging from 1.5-5 per 100,000 population • Median survival from diagnosis of metastases in patients requiring palliative chemotherapy is poor and in the range of 12-18 months, with less than 10% surviving 5 years
Current Standard Treatment	• Therapeutic options are limited for patients with advanced STS • Standard chemotherapy agents include doxorubicin and ifosfamide. Second-line agents include docetaxel, gemcitabine and trabectedin.
Limitations of Current Therapy	• Standard chemotherapy agents, such as doxorubicin and ifosfamide produce objective response in 20-30% of patients, with stable disease in a further 30-40%. • Toxicities of these agents are often substantial. Ifosfamide is often given as multiday infusions with associated hydration and mesna to reduce toxicity. Similar issues related to IV administration and toxicities occur with the commonly used second-line agents.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)	Dr. Bill Evans, Oncologist
Dr. Maureen Trudeau, Oncologist (Vice-Chair)	Dr. Allan Grill, Family Physician
Dr. Chaim Bell, Economist	Dr. Paul Hoskins, Oncologist
Dr. Scott Berry, Oncologist	Danica Lister, Pharmacist
Bryson Brown, Patient Member	Carole McMahon, Patient Member Alternate
Mario de Lemos, Pharmacist	Jo Nanson, Patient Member
Dr. Sunil Desai, Oncologist	Dr. Peter Venner, Oncologist
Mike Doyle, Economist	Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Chaim Bell who was not present at this meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the final recommendation except:

- Dr. Chaim Bell who was not present at this meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pazopanib for soft tissue sarcoma, through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

The pERC Final Recommendation may also be informed by feedback on the pERC Initial Recommendation from pCODR's Provincial Advisory Group, patient advocacy groups that provided input at the beginning of the review and the Submitter and/or the manufacturer of the drug under review if they were not the Submitter. Feedback on the pERC Initial Recommendation that was considered is posted on the pCODR website.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).