

pCODR EXPERT REVIEW COMMITTEE (pERC) INITIAL 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.

Providing Feedback on this Initial Recommendation

Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this 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 Issued:
October 4, 2012

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) does not recommend funding pazopanib (Votrient) in patients with soft tissue sarcoma. The Committee acknowledged the need for effective treatments for patients with STS, however, it made this recommendation because, as compared with placebo, pazopanib conferred only a very 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 limited treatment options for soft tissue sarcoma (STS) and that there is a need for effective treatments with reduced toxicities 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 deliberated upon the results from the PALETTE study and considered that although pazopanib, as compared with placebo, provides some clinical benefit for patients in terms of delaying progression, there was no measured net clinical benefit in improved length or quality of life. 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) and that outcomes of overall survival and quality of life are very important for this patient population. 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. pERC considered it challenging to interpret the toxicity of pazopanib as it was compared with placebo and not with other therapies that may be used in clinical practice. However, pERC noted that no unexpected adverse events were noted for pazopanib in the PALETTE study.

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 reduced toxicity compared with current therapies. pERC noted that an overall survival benefit was not observed in PALETTE and that the toxicity of pazopanib compared with current 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 used in the treatment of soft tissue sarcoma. Therefore, overall, pERC considered that pazopanib partially aligned with patient values.

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 that they provided. However, pERC considered that at the range of estimates identified, pazopanib was not cost-effective.

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.

[pERC's Deliberative Framework](#) for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

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) and input from pCODR's Provincial Advisory Group.

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.

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 bias results. Therefore, although global quality of life scores were similar between pazopanib and placebo, pERC considered that these data should be interpreted with caution.

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.

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 convenience of treatment

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 treatment options can be difficult 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.

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 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 based 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 may be more convenient for 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 may 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. Pazopanib is not indicated for GIST and adipocytic soft tissue sarcomas.
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 common 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

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.

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*.

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.

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