

## pCODR EXPERT REVIEW COMMITTEE (pERC) INITIAL RECOMMENDATION on RESUBMISSION

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 hydrochloride (Votrient)

#### Submitter's Funding Request:

First-line therapy in patients with metastatic renal cell (clear cell) carcinoma with good performance status (ECOG 0-1)

#### Submitted By:

GlaxoSmithKline Inc.

#### Manufactured By:

GlaxoSmithKline Inc.

#### NOC Date:

May 27, 2010

#### Resubmission Date:

February 20, 2013

#### Initial Recommendation Issued:

July 5, 2013

### pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding pazopanib hydrochloride (Votrient) for patients with advanced or metastatic clear cell renal carcinoma as an alternative treatment option to sunitinib for patients with good performance status. pERC made this recommendation because, based on two randomized studies directly comparing pazopanib and sunitinib, the efficacy of the two therapies may be similar, the toxicity profiles of the two therapies differ and there is a need for patients to have other treatment options. In addition, pazopanib is cost-effective relative to sunitinib, assuming similar efficacy, standard dosing and the current list prices of the two therapies.

### POTENTIAL NEXT STEPS FOR STAKEHOLDERS

#### Options for Utilization Management

Provinces should be aware that provincial drug spending may increase if pazopanib were to be used in patients with disease progression on sunitinib. pERC did not support funding pazopanib in this setting since there are no randomized studies evaluating pazopanib in these patients and evidence-based treatment options already exist for these patients, e.g. everolimus, axitinib.

## SUMMARY OF pERC DELIBERATIONS

pERC noted that the current standard of care and most relevant comparator in the first-line treatment of advanced or metastatic renal cell carcinoma is sunitinib. The two randomized controlled trials included in the pCODR systematic review, the COMPARZ study and the PISCES study compared pazopanib with sunitinib. While the COMPARZ study provided key evidence on efficacy outcomes, the PISCES study was a supportive trial providing evidence on patient preferences for the two therapies. pERC also noted the original pCODR submission was based on Study VEG105192, a randomized controlled trial comparing pazopanib with placebo and pERC had previously concluded that there was a net clinical benefit of pazopanib compared with placebo.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberations focused on the results from the COMPARZ study. It was noted that this was a non-inferiority trial whose primary outcome was progression-free survival as assessed by an independent review committee. pERC noted that median progression-free survival appeared similar between pazopanib and sunitinib and not statistically significantly different. Non-inferiority of the two treatments was demonstrated in the intention-to-treat (ITT) analysis (HR=1.05, 95% CI 0.90 to 1.22) based on a non-inferiority margin of 1.25, which was defined *a priori*. pERC noted that in the per protocol analysis the HR of 1.07, and a 95% CI of 0.91 to 1.26 was observed and further noted that the upper bound of this confidence interval was slightly higher than the non-inferiority margin that had been set in the ITT analysis. pERC considered there to be a lack of consistency demonstrated in these results and noted that a per protocol analysis may be considered to be a more conservative analysis. Therefore, pERC was challenged in determining how to interpret the results of the COMPARZ study. pERC also discussed other methodological concerns related to the COMPARZ trial including challenges for interpreting quality of life assessments and the inclusion of patients from a concurrently running Asian study to increase sample size. pERC noted that, to date, results of COMPARZ have not yet been published in a peer-review journal and widely scrutinized by practicing oncologists. As a result of these factors, pERC encountered some uncertainty in assessing the clinical benefit of pazopanib relative to sunitinib. However, pERC concluded that they were clinically comparable treatments and that it was probable pazopanib and sunitinib have similar efficacy.

The Committee also discussed the safety of pazopanib relative to sunitinib based on the results of the COMPARZ and PISCES studies. pERC noted the data supported that the two treatments had different toxicity profiles. Also, adverse events associated with pazopanib appeared to be tolerable. Among the most frequent adverse events in the COMPARZ study, diarrhea, hypertension, hair color changes and hepatotoxicity were more common in pazopanib patients while fatigue, hand-foot syndrome, stomatitis, altered taste, thrombocytopenia and neutropenia were more common in sunitinib patients.

pERC discussed the alignment of pazopanib with patient values. The Committee noted that side effects associated with sunitinib, such as hand-foot syndrome, are a concern to patients and may impact on quality of life. As a result, patients have expressed a need for additional treatment options. pERC noted that providing pazopanib as an alternative treatment option to sunitinib would align with these patient values. However, pERC emphasized that the selection of the appropriate treatment option should be based on the assessment of the treating physician, taking into consideration the concerns of the patient.

pERC also deliberated upon the potential use of pazopanib in patients with disease progression on sunitinib. It was noted that there were no randomized controlled trials evaluating pazopanib in this patient population. In addition, the Committee discussed comments from the Provincial Advisory Group that use of pazopanib following other tyrosine kinase inhibitors may impact adoption feasibility by increasing the budget impact of pazopanib. pERC noted that the current standard of care for second-line treatment of advanced or metastatic renal cell carcinoma is everolimus and concluded that there was insufficient reason to support pazopanib use in this setting as everolimus has been studied in patients with metastatic renal cell carcinoma and disease progression on a tyrosine kinase inhibitor.

pERC also deliberated upon the cost-effectiveness of pazopanib versus sunitinib. pERC noted that cost-effectiveness estimates provided by the pCODR Economic Guidance Panel (EGP), which assumed similar efficacy to sunitinib, indicated that there were potential cost savings associated with pazopanib. pERC also discussed that the EGP's best estimates were based on the current list prices of pazopanib and sunitinib. It was noted that if the unit price of sunitinib were reduced, the ability of pazopanib to be cost saving at the submitted list price could be substantially diminished. However, pERC noted that assuming standard dosing and the current list prices of the two therapies, pazopanib is cost-effective compared with sunitinib.

## CONTEXT OF THE RESUBMISSION

A submission for pazopanib (Votrient) for patients with metastatic renal cell carcinoma was previously received by pCODR on November 3, 2011 and the pERC Final Recommendation was issued on January 5, 2012.

- The pERC Final Recommendation was to fund pazopanib hydrochloride (Votrient) in patients with advanced or metastatic clear cell renal carcinoma who, based on the mutual assessment of the treating physician and the patient, are unable to tolerate ongoing use of an effective dose of sunitinib. The committee made this recommendation because there was too much uncertainty in the similarity of effectiveness between pazopanib and sunitinib as the results of the pivotal study, VEG105192 (Sternberg 2010), did not have direct comparative evidence to sunitinib. However, the committee noted the need for other options among patients unable to tolerate sunitinib.
- As a potential next step for stakeholders, pERC noted the possibility for a Resubmission using data from two ongoing studies directly comparing pazopanib and sunitinib, COMPARZ and PISCES. These studies would provide information on comparative efficacy and patient preferences that could lead to a recommendation for funding in a broader patient population if a resubmission were made to pCODR.
- The Resubmission that was made by the manufacturer provided New Information on pazopanib. The New Information included:
  - Clinical data from two randomized controlled trials (COMPARZ and PISCES), identified by pERC as potentially being able to address points previously raised in the Final Recommendation
  - A revised economic evaluation

## 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 (Kidney Cancer 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 compared to sunitinib on patient outcomes in the treatment of patients with advanced or metastatic RCC who had received no prior systemic therapies or who had received prior treatment with cytokines.

### Studies included

The pCODR systematic review included two randomized controlled trials, COMPARZ and PISCES, both of which are currently unpublished.

- COMPARZ (unpublished) was an open-label, parallel group randomized controlled trial (N=1110), evaluating the non-inferiority of pazopanib (800 mg po daily) compared with sunitinib (50 mg po daily, 6 weeks on and 2 weeks off). Non-inferiority was based on achieving a non-inferiority margin of 1.25 based on the outcome of progression-free survival.
- PISCES (unpublished) was a 22-week double-blind, cross-over trial (N=168) evaluating patient preference for pazopanib compared with sunitinib based on a questionnaire assessment.

pERC noted that during the COMPARZ study, due to unexpectedly high rates of drop-out and discordance between the independent review committee and investigators in adjudicating outcomes, the COMPARZ protocol was amended to increase its sample size and include all 183 patients randomized to a concurrently running Asian trial (VEG113078) of similar design. pERC discussed that this was unusual and considered that this may have an impact on the methodological quality of the study.

**Patient populations: predominantly clear cell carcinoma, good performance status**

pERC noted that the patient populations in the COMPARZ and PISCES studies were similar. The majority of patients in both studies had good performance status, as measured by either ECOG performance status categories or Karnofsky performance scale categories. Almost all of the patients in COMPARZ and 90% of patient in PISCES had clear cell or predominantly clear cell carcinoma.

**Key efficacy results: differences between ITT and per protocol analyses**

Key efficacy outcomes deliberated upon by pERC included progression-free survival based on independent review committee assessment, which was the primary outcome in the COMPARZ study and overall survival.

pERC discussed that median progression-free survival in the COMPARZ study appeared similar between pazopanib and sunitinib and not statistically significantly different. However, because COMPARZ was designed to evaluate non-inferiority of the two treatments, a pre-specified non-inferiority margin of 1.25 needed to be met and this threshold was only defined in the ITT analysis. While non-inferiority was achieved in the intention-to-treat (ITT) analysis, pERC noted that the results differed from the PP analysis.

- In the intention-to-treat analysis a HR of 1.05 and a 95% CI, 0.90 to 1.22 was observed, with a median progression-free survival of 8.4 months compared with 9.5 months in sunitinib-treated patients. Therefore, non-inferiority was achieved because the upper bound of this confidence was below the *a priori defined* threshold of 1.25.
- In the per-protocol analysis a HR of 1.07, and a 95% CI of 0.91 to 1.26 was observed [median progression-free survival of 8.4 months for pazopanib compared with 10.2 months in sunitinib-treated patients] pERC noted that the upper bound of this confidence interval was slightly higher than the non-inferiority margin that had been set in the ITT analysis.

pERC considered these possible inconsistencies between the intention-to-treat and per-protocol analyses and therefore was not confident that it could unambiguously conclude that the two drugs are non-inferior. pERC also noted that when evaluating non-inferiority, the per protocol analysis is the more conservative analysis. Therefore, pERC had challenges determining how to interpret the results of the COMPARZ study. pERC discussed the uncertainty these results created in assessing the clinical benefit of pazopanib relative to sunitinib. However, pERC considered that the two therapies were clinically comparable treatments and that it was probable pazopanib and sunitinib have similar efficacy.

pERC also noted that overall survival was similar in both the pazopanib and sunitinib groups (28.4 months versus 29.3 months, respectively,  $P > 0.05$ ).

**Safety: Toxicity profiles differ for pazopanib and sunitinib**

The Committee also discussed the safety of pazopanib relative to sunitinib based on the results of the COMPARZ and PISCES studies. pERC noted that the data supported that the two treatments had different toxicity profiles. Also, adverse events associated with pazopanib appeared to be tolerable. Overall, the proportion of patients with a serious adverse event was similar between the pazopanib and sunitinib groups although the type of serious adverse event differed between groups. Among the most frequent adverse events observed in the COMPARZ study, diarrhea, hypertension, hair color changes and hepatotoxicity were more common in pazopanib patients while fatigue, hand-foot syndrome, stomatitis, altered taste, thrombocytopenia and neutropenia were more common in sunitinib patients. pERC noted from the patient advocacy group input, that sunitinib-related adverse events such as hand-foot syndrome were a serious concern for some patients and may impact on patients' quality of life.

### **Quality of life: important to patients**

pERC discussed quality of life and patient preference outcomes from the COMPARZ and PISCES trials. pERC noted that quality of life is an outcome valued by patients but that there were challenges interpreting the quality of life and patient preference data from these studies.

### **Need: new therapies with improved efficacy and safety and a choice of treatment options**

pERC noted that metastatic renal cell carcinoma has an unfavourable prognosis with few patients surviving longer than five years. Therefore, there is a need for novel therapies in the treatment of metastatic renal cell carcinoma, which have increased efficacy and safety. While sunitinib is considered standard first-line therapy in Canada, it is not curative and is associated with important side effects. pERC noted that COMPARZ was a non-inferiority trial, which was not designed to demonstrate that pazopanib has improved efficacy or safety. However, the Committee considered that there may be a need for a different treatment options in patients who are unable to tolerate sunitinib due to side effects such as hand-foot syndrome. pERC noted that providing pazopanib as an alternative treatment option would meet this need because pazopanib is associated with less hand-foot syndrome and has a different side effect profile compared with sunitinib.

pERC also considered there may be a need for a different treatment option in patients whose disease has progressed while taking sunitinib. However, everolimus is a standard treatment option for these patients. There is no randomized controlled trial evidence evaluating pazopanib in this setting and possible sequential use of pazopanib may create barriers for the Provincial Advisory Group when implementing a recommendation.

## **PATIENT-BASED VALUES**

### **Values of patients with metastatic renal cell carcinoma: Maintaining quality of life**

Patient advocacy group input noted that there is no cure for patients with metastatic renal cell carcinoma and that from a patient perspective, quality of life while living with metastatic renal cell carcinoma is one of the most important considerations. Therefore, pERC concluded that pazopanib's favorable side effects profile on the most frequent TKI-related adverse events aligned with the patient values of improving quality of life.

### **Patient values on treatment: Seeking choice and alternate side effect profile**

pERC noted that currently available agents for metastatic renal cell carcinoma can cause significant adverse effects in some patients. Patient advocacy group input from Kidney Cancer Canada indicated that although sunitinib and other tyrosine kinase inhibitors are considered effective, they have associated side effects which some patients, in varying degrees, find difficult to manage. Patients consider that having pazopanib as an alternative treatment choice may provide a more manageable treatment option for some individuals. pERC discussed these patient values when considering safety data on pazopanib from the COMPARZ and PISCES studies. pERC noted that pazopanib was associated with less hand-foot syndrome, which is a side effect of concern to patients. Therefore, providing pazopanib as an alternative treatment option to sunitinib would align with these patient values.

pERC also noted that patients place importance on being able to select, together with their doctors, which drugs are better suited to their circumstances and that having a choice of treatments was an important patient-value. However, pERC emphasized that the selection of the appropriate treatment option should be based on the assessment of the treating physician, taking into consideration the concerns of the patient.

## **ECONOMIC EVALUATION**

### **Economic model submitted: Cost-effectiveness and cost-utility analysis**

pCODR assessed an economic evaluation looking at the cost-effectiveness and cost-utility of pazopanib compared with sunitinib in the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma who have received no prior systemic therapy. pERC considered this was an appropriate comparison as sunitinib is the standard first-line therapy in patients with metastatic renal cell carcinoma.

### **Basis of the economic model: Clinical and economic inputs**

Costs include drug treatment costs, administration costs, dispensing costs, other costs associated with pazopanib and sunitinib treatments such as hospitalizations and specialist's visits, the cost associated with adverse events, the cost of routine care and follow-up, and the cost of post-treatment anti-cancer therapy for pazopanib and sunitinib.

Clinical effects were based on overall survival and investigator-assessed PFS from the ITT analysis of the COMPARZ study. Utility values were based on EQ-5D assessments from the PISCES trial.

### **Drug costs: uncertainty in drug prices and effects of dosing**

At the list price, pazopanib costs \$37 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 \$148 and the average cost per 28-day course is \$4,144.

At the list price, sunitinib costs \$62, \$124 or \$248 per 12.5mg, 25mg and 50mg capsule, respectively. At the recommended dose of 50 mg per day, the average cost per day in a 28-day course of sunitinib is \$165 and the average cost per 28-day course is \$4,632.

pERC discussed the current list prices of pazopanib and sunitinib and discussed the potential uncertainty associated with these prices. It was also noted that there may be uncertainty about the drug costs due to dose modifications that commonly occur in clinical practice (e.g., dose reductions due to adverse events, continuous dosing of sunitinib). pERC noted the EGP's reanalyses examining possible reductions in sunitinib pricing. It was noted that if the unit price of sunitinib were reduced, the ability of pazopanib to be cost saving at the submitted list price could be substantially diminished.

### **Cost-effectiveness estimates: potential for cost savings associated with pazopanib**

pERC deliberated upon the cost-effectiveness of pazopanib versus sunitinib. pERC noted that cost-effectiveness estimates provided by both the pCODR Economic Guidance Panel (EGP) and the manufacturer indicated that there were potential cost savings associated with pazopanib.

pERC discussed that the EGP's reanalyses assumed equal efficacy and impact on quality of life for pazopanib and sunitinib. pERC noted that if similar efficacy is assumed for pazopanib and sunitinib then a cost minimization approach could also be taken in the economic analysis.

pERC also discussed that the EGP's best estimates were based on the current list prices of pazopanib and sunitinib and if pricing were to change, the cost-effectiveness of pazopanib could change. However, pERC noted that at the current list prices of the two therapies and assuming standard dosing, pazopanib is cost-effective compared with sunitinib.

## **ADOPTION FEASIBILITY**

### **Considerations for implementation and budget impact: confidential prices, treatment sequencing and dose modifications**

pCODR's Provincial Advisory Group noted the relative costs of pazopanib and sunitinib would be a key consideration. pERC discussed the potential for confidential prices of pazopanib and sunitinib and noted that this introduced considerable uncertainty into the economic analysis.

pCODR's Provincial Advisory Group input also pointed out the possibility of sequential use of pazopanib, which may increase budget impact. pERC noted there is no clinical trial evidence to support use of pazopanib if patients experience disease progression on sunitinib while everolimus is an evidence-based treatment option in this patient population.

pCODR's Provincial Advisory Group input indicated that jurisdictions have observed dose de-escalations with sunitinib treatment and considered that this may occur with pazopanib as well. pERC considered that this could impact drug costs and introduce further uncertainty into cost-effectiveness estimates.

## DRUG AND CONDITION INFORMATION

<b>Drug Information</b>	<ul style="list-style-type: none"> <li>Multi-target tyrosine kinase inhibitor</li> <li>200 mg tablets reviewed by pCODR</li> <li>Recommended dosage of 800 mg administered orally once daily</li> </ul>
<b>Cancer Treated</b>	<ul style="list-style-type: none"> <li>Advanced or metastatic renal cell carcinoma with clear-cell histology</li> </ul>
<b>Burden of Illness</b>	<ul style="list-style-type: none"> <li>Kidney cancer accounts for approximately 3% of malignant diseases in Canada with approximately 90-95% being renal cell carcinoma. The prognosis for patients with metastatic disease is poor with few surviving longer than five years.</li> </ul>
<b>Current Standard Treatment</b>	<ul style="list-style-type: none"> <li>Sunitinib, another tyrosine kinase inhibitor, is considered the standard first-line therapy in Canada.</li> <li>Everolimus, an mTOR inhibitor, is considered standard second line therapy after failure of first-line tyrosine kinase inhibitor therapy</li> <li>Axitinib, a multi-target tyrosine kinase inhibitor, is also approved in the second line setting for patients who have a contraindication to everolimus.</li> </ul>
<b>Limitations of Current Therapy</b>	<ul style="list-style-type: none"> <li>Current therapies are not curative and patients may experience significant side effects</li> </ul>

## 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. Maureen Trudeau, Oncologist (Vice-Chair)  
 Dr. Chaim Bell, Economist  
 Dr. Scott Berry, Oncologist  
 Bryson Brown, Patient Member  
 Mario de Lemos, Pharmacist  
 Dr. Sunil Desai, Oncologist  
 Mike Doyle, Economist

Dr. Bill Evans, Oncologist  
 Dr. Allan Grill, Family Physician  
 Dr. Paul Hoskins, Oncologist  
 Danica Lister, Pharmacist  
 Carole McMahon, Patient Member Alternate  
 Jo Nanson, Patient Member  
 Dr. Peter Venner, Oncologist  
 Dr. Tallal Younis, Oncologist

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

- Dr. Peter Venner who was excluded from voting due to a conflict of interest
- Jo Nanson, Dr. Chaim Bell, Dr. Scott Berry, Dr. Bill Evans and Dr. Sunil Desai who were not present

### 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 metastatic renal cell carcinoma, through their declarations, eight members had a real,

potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one 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*. There is no non-disclosable information in this publicly available report.

#### **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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