The pCODR Expert Review Committee (pERC) recommends funding pazopanib hydrochloride (Votrient) for 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. Funding in a broader patient population was not recommended because there is too much uncertainty, due to the lack of direct evidence from randomized comparative trials, that the effectiveness of pazopanib is similar to sunitinib; however, there is a need for other options among patients unable to tolerate sunitinib. Therefore, while current evidence is insufficient to recommend funding broadly, from a clinical perspective, it suggests that pazopanib could have similar efficacy, better tolerability and may be cost-effective relative to sunitinib, assuming similar pricing and standard dosing of the two therapies. This led pERC to recommend pazopanib for the defined population of patients who are unable to tolerate sunitinib.

Possibility of Resubmission to Support Funding in Broader Population
There are two ongoing studies directly comparing pazopanib and sunitinib, COMPARZ and PISCES. These studies will 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.

Options for Utilization Management
Provinces should be aware that provincial drug spending may increase if there were to be use of pazopanib 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.
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. However, the one randomized controlled trial included in the pCODR systematic review compared pazopanib with placebo (Study VEG105192, Sternberg 2010). As a result, pERC encountered considerable uncertainty when trying to determine the relative effectiveness and safety of pazopanib versus sunitinib.

Given the lack of a relevant comparator in the main pazopanib study, pERC placed progression-free survival and overall survival results from Study VEG105192 in the context of results from a randomized controlled trial comparing sunitinib with interferon (Motzer 2007) as well as an indirect comparison that informed the clinical effect estimates in the economic analysis (Kilonzo 2010). This led pERC to consider the possibility that pazopanib and sunitinib may have similar efficacy. The Committee had concerns that interpretations based on cross-trial and indirect comparisons are uncertain on the magnitude and direction of benefit.

pERC discussed that results from an ongoing study comparing pazopanib and sunitinib (COMPARZ) will provide more certainty regarding the relative effectiveness of the two treatments. Given the uncertainty in the effectiveness of pazopanib relative to other available targeted therapies used to treat advanced or metastatic renal cell carcinoma, pERC did not support funding pazopanib as a first-line treatment in all patients with advanced or metastatic renal cell carcinoma. However, pERC determined that when considering need and the availability of effective alternatives, there may be a smaller patient population that could benefit from access to pazopanib. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer but noted that none of this feedback was able to reduce the uncertainty that pERC experienced in interpreting the evidence associated with pazopanib.

The Committee also interpreted safety data on pazopanib in the context of cross-trial and indirect comparisons with sunitinib and encountered similar uncertainty. The Committee noted that in an indirect comparison, pazopanib had statistically significantly less fatigue compared with sunitinib but that no other statistically significant differences in adverse events were reported. This led pERC to consider the possibility that pazopanib may have a more favourable side effect profile. In further reflecting on the safety of pazopanib and the current clinical context, the Committee noted that side effects such as hand-foot syndrome are associated with sunitinib and are a concern to patients. In the randomized controlled trial comparing pazopanib with placebo, the proportion of patients reporting hand-foot syndrome was less than 10%, which the Committee considered to be low. Therefore, pERC considered that providing pazopanib as an option in patients who are intolerant to sunitinib may meet a specific need for some patients and would align with patient-expressed values of having more treatment options and potentially less side effects than with currently available drugs. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed patient advocacy group feedback regarding how intolerance to sunitinib could best be defined for funding purposes and how patient care could be impacted by the definition of intolerance. pERC noted that it was important that the determination of intolerance to sunitinib 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 whose disease has progressed while taking 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 with disease progression on a tyrosine kinase inhibitor.
Finally, pERC deliberated upon the cost-effectiveness of pazopanib. pERC determined that due to the uncertainty of the clinical effectiveness of pazopanib relative to sunitinib, the cost-effectiveness of pazopanib was also uncertain. However, when considering a number of estimates and ranges of cost-effectiveness including the manufacturer’s estimate of $57,309 per quality-adjusted life year for pazopanib versus sunitinib, pERC recognized that there is a possibility that pazopanib could be cost-effective as a first-line therapy. This estimate was based on a confidential price for pazopanib and a 10% reduction from the list price for sunitinib. The Committee noted that the possibility of confidential pricing arrangements for pazopanib and sunitinib introduced further uncertainty into the cost-effectiveness estimates. The Committee recognized that the cost-effectiveness estimates in the economic evaluation did not apply to patients who are intolerant to sunitinib. They discussed that there is currently no clinical data on the effectiveness of pazopanib in these patients but also concluded that there is limited merit in trying to collect these data simply to inform this recommendation.

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 panel,
- input from one patient advocacy group (Kidney Cancer Canada),
- input from pCODR’s Provincial Advisory Group,
- feedback on the pERC Initial Recommendation from
  - the one patient advocacy group who provided input at the beginning of the review (Kidney Cancer Canada),
  - pCODR’s Provincial Advisory Group,
  - the Submitter (GlaxoSmithKline Inc.).

The pERC Initial Recommendation was to recommend funding in patients with advanced or metastatic clear cell renal carcinoma who are unable to tolerate sunitinib. Feedback on the pERC Initial Recommendation indicated that pCODR’s Provincial Advisory Group agreed with the recommendation and that Kidney Cancer Canada and GlaxoSmithKline Inc. agreed with the recommendation in part.

OVERALL CLINICAL BENEFIT

pCODR review scope
The pCODR reviewed the use of pazopanib compared with standard therapy or placebo for the treatment of patients with advanced or metastatic renal cell carcinoma who have received no prior systemic therapies or who have received prior treatment with cytokines.

Studies included
The pCODR systematic review included one double-blind, randomized controlled trial (Study VEG105192, Sternberg 2010) comparing pazopanib with placebo in patients with advanced and/or metastatic renal cell carcinoma who were treatment naive or who had received one prior cytokine-based systemic therapy. pERC recognized that at the time the trial was designed, placebo may have been an appropriate comparator; however, sunitinib is now the standard of care for the first-line treatment of metastatic renal cell carcinoma in Canada.

The pCODR review also provided contextual information on relevant comparators including sunitinib (indirect comparison by Kilonzo 2010; randomized controlled trial by Motzer 2007) and on the validity of progression-free survival as a surrogate for overall survival in metastatic renal cell carcinoma (retrospective analysis by Heng 2011).
Patient populations: Good performance status patients included
Study VEG105192 (Sternberg 2010) included only patients with an ECOG score of 0 or 1, representing patients with good performance status. pERC noted that this represented a relatively high-functioning patient population who may not be willing to tolerate increased severity or frequency of side effects compared with existing treatments. The Committee also discussed that willingness to tolerate adverse events ranges widely among patients, as outlined in input received from the patient advocacy group, Kidney Cancer Canada.

Key efficacy results: Improved progression-free survival
Key efficacy outcomes deliberated upon by pERC included progression-free survival and overall survival. In Study VEG105192 (Sternberg 2010) patients treated with pazopanib demonstrated a statistically significant improvement in median progression-free survival compared with placebo (9.2 months versus 4.2 months, hazard ratio (HR) = 0.46, P < 0.0001) but overall survival was not statistically significantly different between the two treatment arms. The Committee discussed that it would be difficult to obtain statistically significant overall survival results given the high rate of cross-over in the placebo arm of the trial (54%). pERC noted that there are limitations with using progression-free survival as an outcome but that observational data from a recent retrospective study by Heng et al. (2011) suggests that progression-free survival may predict overall survival in patients with metastatic renal cell carcinoma.

Quality of life: Similar quality of life for pazopanib and placebo
Changes in quality of life were similar between pazopanib and placebo in Study VEG105192 (Sternberg 2010). pERC noted that maintaining quality of life was valued by patients as outlined in the patient advocacy group input received from Kidney Cancer Canada. pERC also considered that the lack of difference between pazopanib and placebo patients may be an indication that side effects of pazopanib are tolerable.

Safety: Low incidence of hand-foot syndrome
Known tyrosine kinase inhibitor-associated adverse events such as hand-foot syndrome, mucositis/stomatitis, proteinuria, thrombocytopenia, and hypothyroidism occurred with an incidence less than 10% each, with grade three and grade four adverse events reported in less than 1% of patients who received pazopanib in Study VEG105192. pERC discussed that the low incidence of hand-foot syndrome with pazopanib may be a benefit for patients, particularly those who are unable to tolerate sunitinib.

Limitations: No direct comparison with sunitinib but trials ongoing
The main limitation identified by pERC in the evidence for pazopanib is that there are no randomized controlled trials directly comparing it with sunitinib, the current standard of care. pERC noted that there are two ongoing trials that will provide important comparative data when they are completed. COMPARZ (NCT 00720941) is an open-label randomized controlled trial comparing pazopanib with sunitinib and PISCES (NCT 01064310) is a double-blind randomized cross-over trial comparing patient preferences for pazopanib versus sunitinib. Upon reconsideration of the pERC Initial Recommendation, the Committee noted that none of the feedback was able to reduce the uncertainty that pERC experienced in interpreting the clinical evidence for pazopanib. pERC emphasized that there remained significant uncertainty in both the overall survival results and progression-free survival results in the absence of a direct comparison with sunitinib, the current standard of care. While pERC recognized that patient advocacy group feedback expressed concern about a delay in access until the results of COMPARZ were available, the Committee noted that the trial is in progress and that until results are available, some access, in a smaller patient population that could benefit from pazopanib, would be appropriate.

Comparator information: Uncertain results of indirect comparisons with sunitinib
pERC discussed the results of one randomized controlled trial comparing sunitinib with interferon (Motzer 2007) and noted that statistically significant differences in progression-free survival and overall survival were observed. The Committee remarked that making and interpreting cross-trial comparisons with Study VEG105192 was challenging, particularly given the use of different comparators in the two trials.

An indirect comparison of first-line treatments of patients with advanced and/or metastatic renal cell carcinoma, including pazopanib, sunitinib, interferon-α or best supportive care (Kilonzo 2010) was also considered by pERC. Estimates of progression-free survival and overall survival were similar between pazopanib and sunitinib but pazopanib demonstrated statistically significantly less fatigue than sunitinib (HR = 0.21, 95% confidence interval (CI): 0.06 to 0.77). No other statistically significant differences in
adverse events were observed. pERC discussed the limitations of relying on indirect evidence and noted that there was considerable uncertainty associated with these results, which were highly dependent on the selection of studies included in the indirect comparison.

**Need: Intolerance to sunitinib or progression on sunitinib considered**

pERC 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. pERC also considered there may be a need for a different treatment option in patients who are unable to tolerate sunitinib. Upon reconsideration of the pERC Initial Recommendation, the Committee emphasized that there is a differentiation between patients with intolerance to sunitinib and patients experiencing disease progression while taking sunitinib.

**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. pERC noted this patient value and discussed quality of life results comparing pazopanib with placebo in Study VEG105192 (Sternberg 2010) and considered that pazopanib did not decrease quality of life. In addition, quality-of-life estimates were incorporated into the economic evaluation and the Committee considered quality-adjusted life year estimates when deliberating upon cost-effectiveness.

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

Patient advocacy group input indicated that currently available agents for metastatic renal cell carcinoma can cause significant adverse effects in some patients. Patient 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 and pERC gave particular importance to information on hand-foot syndrome and fatigue that suggested the possibility that pazopanib could have a more favourable side effect profile compared with sunitinib. Upon reconsideration of the pERC Initial Recommendation and patient advocacy group feedback, pERC discussed that it is difficult to pre-determine which patients will experience significant adverse effects while taking sunitinib.

Patient advocacy group input indicated 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. pERC deliberations considered this when trying to define a patient population for whom there was a need for pazopanib, despite the uncertainty around the comparative effectiveness of pazopanib and sunitinib.

**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 choice of first-line therapy in patients with metastatic renal cell carcinoma.
Basis of the economic model: Clinical and economic inputs
Costs include treatment, healthcare, administration/dispensing and adverse event costs. Clinical effects were based on an indirect comparison (Kilonzo 2010) that included one pazopanib study versus placebo (N=233), one sunitinib study versus interferon (N=750) and five interferon studies versus placebo (N=1014).

Drug costs: Uncertainty in drug prices and effects of dosing
Pazopanib costs $41.00 per 200 mg oral tablet at the list price and $xxxxx at the submitted confidential price. (Non-disclosable economic information was provided to pERC in the pCODR guidance reports for deliberation on a recommendation and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.) At the list prices and over a 28 day treatment course, the average cost per day in a course is $164.00 for pazopanib and $165.43 for sunitinib. The main economic analysis assumed a 10% reduction in the list price of sunitinib. pERC discussed the prices of pazopanib and sunitinib and noted that there is considerable uncertainty due to possible confidential pricing arrangements for both drugs. There is also 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). When the cost of pazopanib did not change but the cost of sunitinib was reduced, cost-effectiveness results for pazopanib were less favourable.

Clinical effect estimates: Uncertainty in clinical effectiveness
The key variables in the economic model that influenced results were clinical treatment effects (i.e., estimates of overall survival and progression-free survival from the indirect comparison) and treatment costs that are influenced by estimates of clinical effectiveness. pERC discussed the uncertainty of cost-effectiveness estimates in the absence of direct evidence comparing pazopanib and sunitinib. It was noted there were differences between the eight studies included in the indirect comparison due to different patient populations and that estimates of clinical effectiveness were very sensitive to which studies were included.

Cost-effectiveness estimates: Uncertainty in incremental cost-effectiveness ratio
According to the main economic analysis submitted to pCODR, the incremental cost-effectiveness ratio was estimated to be $57,309 per quality-adjusted life year gained or $38,122 per life year gained. This was based on a confidential price for pazopanib and a 10% reduction from the list price for sunitinib. pERC discussed other ranges presented in the pCODR Economic Guidance Report, and concluded there was considerable uncertainty in the estimate of the incremental cost-effectiveness ratio. Within the range of cost-effectiveness estimates discussed, pERC noted that if similar pricing and standard dosing were assumed, pazopanib may be cost-effective relative to 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 discussed this could impact on drug costs and introduce further uncertainty into cost-effectiveness estimates.
DRUG AND CONDITION INFORMATION

Drug Information
- Multi-target tyrosine kinase inhibitor
- 200 mg tablets reviewed by pCODR
- Recommended dosage of 800 mg administered orally once daily

Cancer Treated
- Advanced or metastatic renal cell carcinoma with clear-cell histology

Burden of Illness
- 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.

Current Standard Treatment
- Sunitinib, another tyrosine kinase inhibitor, is considered the standard first-line therapy in Canada.
- Everolimus, an mTOR inhibitor, is considered standard second line therapy after failure of first-line tyrosine kinase inhibitor therapy

Limitations of Current Therapy
- Current therapies are not curative and patients may experience significant side effects

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 pERC Initial Recommendation except:
- Dr. Chaim Bell and Mario de Lemos who were not present for the meeting
- Dr. Peter Venner who was excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the pERC Final Recommendation except:
- Dr. Peter Venner who was excluded from voting due to a conflict of interest
- 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 metastatic renal cell carcinoma, through their declarations, seven 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.

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 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. GlaxoSmithKline Inc., as the primary data owner, did not agree to the disclosure of the confidential price submitted for pazopanib, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

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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