



pan-Canadian Oncology Drug Review Final Economic Guidance Report

Pazopanib hydrochloride (Votrient) for metastatic renal cell carcinoma

January 5, 2012

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The pan-Canadian Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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This section outlines the technical details of the pCODR Economic Guidance Panel’s evaluation of the economic evidence that is summarized in Section 1. Pursuant to the <i>pCODR Disclosure of Information Guidelines</i> , this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.	
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The manufacturer, **GlaxoSmithKline Inc.**, submitted an economic evaluation to pCODR that assessed the cost-effectiveness of pazopanib as first-line treatment of patients with advanced and/or metastatic RCC who have received no prior systemic therapy, compared with sunitinib. Clinical inputs for the economic evaluation of pazopanib versus sunitinib were derived based on an indirect comparison (see Figure 1, Section 1.3). The indirect comparison was comprised of one pazopanib study versus placebo or best supportive care (BSC) (n=233), one sunitinib study versus interferon- α (n=750) and five interferon studies versus placebo or BSC (n=1014). This indirect comparison was also the basis of clinical information included in an economic evaluation submitted to the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom.

According to the pCODR Genitourinary Clinical Guidance Panel (CGP), sunitinib is the most relevant comparator. The Clinical Guidance Panel considered that sorafenib may be an additional comparator for sunitinib for this first-line indication. The Submitter did not include this comparison in the main economic analysis or in modifications to the main analysis as no randomized controlled trial data are available for sorafenib in patients with treatment-naïve metastatic RCC.

The following factors were considered by **patient advocacy groups** to be important in the review of pazopanib and were relevant to the economic analysis: quality of life, dosage form and adverse event profiles. A full summary of patient advocacy group input is provided in the pCODR Clinical Guidance Report. Factors important to patients were addressed in the economic analysis as follows:

- The Submitter incorporated quality of life in the submitted model by applying utility scores to measure the model outcomes in quality-adjusted life years (QALYs).
- Because pazopanib and sunitinib are both oral tablets no effect of dosage form was reflected in the economic evaluation.
- Adverse events such as diarrhoea, neutropenia and anemia were also considered in the economic evaluation by applying a utility decrement to patients receiving the treatments as well as incorporating a cost for serious adverse events.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for pazopanib, and are relevant to the economic analysis: differences between pazopanib and sunitinib with respect to drug costs, treatment costs, side effects, dose reductions and treatment outcomes. The Submitter modified the main analysis to explore different costs for pazopanib and sunitinib. However, dose reductions were not investigated by the Submitter's main analysis. The Economic Guidance Panel performed reanalyses incorporating dose reductions. The economic model inherently incorporated the differences in treatment outcomes and adverse events profiles.

At the list price, pazopanib costs \$41.00 per 200 mg oral tablet. At the recommended dose of 800 mg daily, the cost of pazopanib is \$164.00 per day in a 28-day course of pazopanib. The manufacturer also submitted a confidential price to pCODR (\$■■■■) per

200 mg tablet), upon which their main analysis was based. *(Non-disclosable economic information was used in this pCODR Guidance Report 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)*. The list price of the most relevant comparator, sunitinib is \$248.14 per 50 mg capsule. The recommended dose of sunitinib is 50 mg daily for four weeks and then two weeks off. The average cost per day in a 28-day course of sunitinib is \$165.43. The effective price of sunitinib may vary across jurisdictions and be lower than the list price if it is based upon a confidential price that is unknown to pCODR. In the main analysis, the manufacturer assumed that in all jurisdictions, the price of sunitinib was 10% lower than its list price.

1.2 Summary of Results

Based on feedback from the pCODR Clinical Guidance Panel, the Economic Guidance Panel's estimate of the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) ranges from being less costly and equally effective (i.e., dominant) to \$57,309 per quality-adjusted life year (QALY) when pazopanib is compared with sunitinib. The Economic Guidance Panel based these estimates on the model submitted by the manufacturer and reanalyses conducted by the Economic Guidance Panel.

The incremental cost-effectiveness ratio (ICER) was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE) compared with sunitinib. The Economic Guidance Panel's estimate of:

- the extra cost (ΔC) of pazopanib ranges from a cost savings of \$1,073 to an extra cost of \$9,223. Costs include treatment, healthcare, administration/dispensing and adverse event costs.
- the extra clinical effect (ΔE) of pazopanib is between 0 (equal QALYs or life-years gained) and 0.049 QALYs gained (2.4 weeks) or 0.074 life-years gained (3.5 weeks).

This range is based on an Economic Guidance Panel reanalysis where:

- The lower estimate of the range assumes equivalent clinical effects between pazopanib and sunitinib based on feedback from the Clinical Guidance Panel;
- The upper estimate of the range assumes clinical effects that are based on the submitted indirect comparison. The indirect comparison estimated a progression-free survival (PFS) hazard ratio of [REDACTED] and [REDACTED] for pazopanib and sunitinib, each versus interferon respectively; the hazard ratio for overall survival was assumed to be [REDACTED] and [REDACTED] for pazopanib and sunitinib, each versus interferon respectively. *(Non-disclosable efficacy information from the economic analysis was used in this pCODR Guidance Report 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)*.

Additional reanalyses conducted by the Economic Guidance Panel using the submitted model showed:

- The pCODR Clinical Guidance Panel considered that the clinical effects of pazopanib and sunitinib appear similar. By assuming equivalent clinical effects for pazopanib and sunitinib, using the confidential price submitted for pazopanib and assuming a 10% reduction in the price of sunitinib from its list price, pazopanib becomes equally effective and less costly.
- The Economic Guidance Panel conducted detailed reanalyses exploring the impact of varying the treatment effects of pazopanib (and other comparators) within the submitted indirect comparison. The results of these reanalyses produced ICERs which ranged from pazopanib being less costly and less effective to having an ICER of up to over \$200,000 per QALY. However, when feedback from the pCODR Clinical Guidance was considered, the Economic Guidance Panel's best estimate used a more narrow range of cost-effectiveness estimates that assumed equivalent clinical effects between pazopanib and sunitinib.
- Further reanalyses were also performed by the Economic Guidance Panel to examine the impact of incremental price reductions to both pazopanib and sunitinib on the ICER. The results for a 5% to 25% price reduction in the cost of pazopanib from the list price led to pazopanib being less costly and more effective (i.e. dominant) when compared to sunitinib. However, a reduction in the cost of sunitinib of 5% to 25% led the ICER of pazopanib to increase in the range of \$119,939 to \$370,735 per QALY. A mutual 5% decrease for both pazopanib and sunitinib led to a decrease of the ICER to \$54,450 per QALY.

According to the economic analysis that was submitted by the manufacturer, when pazopanib is compared with sunitinib:

- The extra cost (ΔC) of pazopanib is \$2,805. These findings are based on clinical effects derived from the submitted indirect comparison. It also used the confidential price submitted for pazopanib and assumed a 10% reduction in the price of sunitinib from its list price.
- The extra clinical effect (ΔE) of pazopanib is 0.049 quality-adjusted life years (2.4 weeks) or 0.074 life years gained (3.5 weeks). These findings are based on clinical effects derived from the submitted indirect comparison. It also used the confidential price submitted for pazopanib and assumed a 10% reduction in the price of sunitinib from its list price.

So, the Submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$57,309 per QALY gained or \$38,122 per life year gained.

When feedback from the pCODR Clinical Guidance Panel was considered, the Economic Guidance Panel's estimates were similar to submitted estimates.

1.3 Summary of Economic Guidance Panel Evaluation

If the Economic Guidance Panel estimates of extra costs (ΔC), extra clinical effects (ΔE) and the ICER differ from the Submitter's, what are the key reasons?

The key reasons for differences in ΔE and the ICER relate to assumptions around clinical effects. The pCODR Clinical Guidance Panel considered that the clinical effects of pazopanib and sunitinib appear similar. Based on the submitted indirect comparison, the Submitter assumed better PFS and better overall survival for pazopanib: the PFS hazard ratio was assumed to be [REDACTED] and [REDACTED] for pazopanib and sunitinib, each versus interferon respectively; the hazard ratio for overall survival was assumed to be [REDACTED] and [REDACTED] for pazopanib and sunitinib, each versus interferon respectively. *(Non-disclosable efficacy information from the economic analysis was used in this pCODR Guidance Report 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).* When the Economic Guidance Panel conducted a reanalysis where equivalent clinical effects were assumed, pazopanib became less costly and equally effective when compared with sunitinib.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Based on patient advocacy group input, factors important to patients were adequately addressed in the submitted economic analysis, including quality of life and adverse event profiles.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes. The model appears appropriate for the purposes of this analysis.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The key variables in the economic model that influenced results were treatment effects (i.e. estimates of overall survival and PFS) and the price of treatment. The manufacturer did not account for heterogeneity of studies included in the submitted indirect comparison, thereby potentially inflating the treatment effect. Economic Guidance Panel reanalyses demonstrate that cost-effectiveness estimates are sensitive to variation of treatment effects. Because the pCODR Clinical Guidance Panel considered that the clinical effects of pazopanib and sunitinib appear similar, based on currently available evidence, this helped resolve some of the uncertainty around clinical effect estimates. Results were also influenced by assumptions around treatment costs. The confidential price of pazopanib was used and a 10% reduction in the list price of sunitinib was applied in the main analysis. When the cost of sunitinib was reduced, cost-effectiveness results for pazopanib were less favourable.

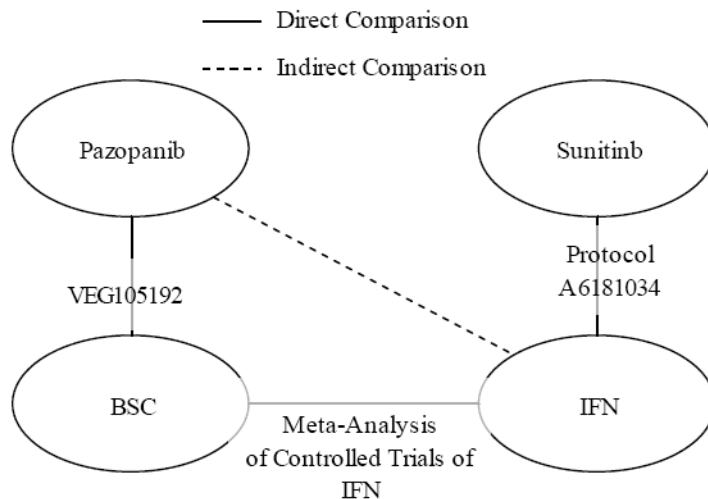
Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the Economic Guidance Panel would have chosen and were they adequate for answering the relevant question?

The Submitter conducted an indirect comparison, using a network meta-analysis approach, to determine treatment effects (Figure 1). The evidence network was comprised of one

pazopanib study versus placebo (n=233), one sunitinib study versus interferon (n=750) and five interferon studies versus placebo (n=1014).

Figure 1: Evidence network used to derive clinical data in economic evaluation

(Note: This figure is derived from the economic evaluation submitted to NICE. The NICE economic model and pCODR economic model are similar.)



The Submitter’s analysis did not adequately account for heterogeneity across the studies included within the evidence network. The Economic Guidance Panel would have conducted a more robust network meta-analysis adjusting for heterogeneity and inconsistency within the evidence network. The Economic Guidance Panel would also have conducted more detailed analyses using different effect estimates for sunitinib (e.g., adjustments to cross-over, intention-to-treat analysis) in their approach. However, based on feedback from the pCODR Clinical Guidance Panel, trials within the evidence network were considered similar enough from a clinical perspective and deemed appropriate for inclusion and adequate for answering the relevant question.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The following variables were considered in the budget impact analysis: incidence of kidney cancer, proportion of patients that are RCC, proportion of patients that are good to moderate risk, eligibility for coverage in public drug plans, impact of attrition, cost of treatments, duration of treatment and dose intensity. The budget impact analysis is most strongly influenced by assumptions around relative costs of treatments. Other variables not considered such as market growth and potential for sequential use could also impact budget impact analysis results had they been considered.

What are the key limitations in the submitted budget impact analysis?

The key limitations in the budget impact analysis relate to assumptions around relative costs of treatment and potential market growth and sequential use.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

1. In the future, using direct evidence from head-to-head trials for pazopanib versus sunitinib would provide more accurate results and minimize the uncertainty arising from the heterogeneity in the submitted network meta-analysis. There are ongoing clinical trials comparing pazopanib directly with sunitinib as first line treatment in metastatic RCC patients (COMPARZ study) and patient preferences between pazopanib and sunitinib (PISCES study).
2. Adjusting the assumed utility values for sunitinib to reflect the actual values as reported in the economic evaluation of sunitinib (Chabot et al.). This would offer a more accurate analysis and reduce uncertainty around the results.

Is there economic research that could be conducted in the future that would provide valuable information related to pazopanib in metastatic RCC?

An assessment of effectiveness and cost-effectiveness of treatment sequences including pazopanib in the treatment of metastatic RCC would provide a more accurate reflection of real-world cost-effectiveness and which may improve estimates of budget impact.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Genitourinary Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of pazopanib (Votrient) for metastatic RCC. The Economic Guidance Report is one source of information that is considered in the pERC Deliberative Framework. The pERC Deliberative Framework is available on the pCODR website (www.pcodr.ca). A full assessment of the clinical evidence of pazopanib (Votrient) for metastatic RCC is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report 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 some economic information, which was provided to pERC for their deliberations, and this information has been redacted in this Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Economic Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies. All members of the pCODR Economic Guidance Panel must comply with the pCODR Conflict of Interest Guidelines; individual Conflict of Interest statements for each member are required on an annual basis and panel members have an obligation to disclose conflicts on an ongoing basis.

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