pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Pazopanib hydrochloride (Votrient) for metastatic renal cell carcinoma

January 5, 2012

Feedback on pERC Initial Recommendation

Name of Drug and Indication(s):	Pazopanib hydrochloride (Votrient) for metastatic renal cell carcinoma
Role in Review:	Manufacturer and Submitter
Organization Providing Feedback:	GlaxoSmithKline Inc.

Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees __X__ agrees in part ____ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*

As part of the GSK submission, an indirect comparison of pazopanib vs. sunitinib was conducted based on Progression Free Survival (PFS) and Overall Survival (OS). The indirect comparisons are calculated using information from the methods specified in: Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

Pazopanib appears to have a comparable efficacy in terms of PFS and OS to Sunitinib. Further, Pazopanib appears to have benefit over interferon (IFN) in both PFS and OS comparable in magnitude to the benefit of Sunitinib over IFN. GSK recognizes that the OS estimates of both Pazopanib vs. IFN and Pazopanib vs. Sunitinib are associated with wide 95% CI. This constitutes the main source of uncertainty in the comparative effectiveness analysis. The magnitude of the variance is primarily driven by the adjustment GSK applied to the OS estimate of Pazopanib vs. Placebo/BSC. The adjustment served to correct for the cross-over in the VEG105192 trial using the weighted unadjusted rank-preserved structural failure time (RPSFT) method with imputation for missing data.

The RPSFT methodology is believed to be the most robust method of assessing the true treatment effect of an active drug in the context of a trial with a high degree of crossover. The RPSFT method yields estimates of the OS among patients randomized to receive placebo assuming that they had not crossed over (i.e. remained on placebo for the duration of the trial). While this adjustment reduces the estimated OS for the placebo group, it increases the variance of the HR for the comparison. It should be noted that a variety of additional analyses also were conducted to assess the potential impact of cross-over on OS. These analyses were conducted in a transparent and conservative manner and in consultation with leading statistical experts. The estimate from the weighted RPSFT analysis was approximately in the middle of the range of estimates generated by these different analyses. The estimated HR for pazopanib vs. IFN of 0.501 as used in our base case analyses is therefore a reasonable point estimate of the likely benefit of pazopanib on OS.

Although OS remains the gold standard for measuring effectiveness of cancer therapies, due to practical and ethical reasons, PFS is often used as the primary efficacy endpoint in such trials. Further, the initial clinical guidance report from pCODR commented on the validity of PFS and OS endpoints as follows:

"The validity of PFS as the primary endpoint for RCC trials is often discussed. Clinically PFS is a very important objective since a period without tumour progression is often associated with a good quality of life for patients. In addition, observational data from Heng et al.[i], 2011 suggests an association between PFS and overall survival. With the availability of various active therapies and the option of crossover within the trials, overall survival has become a difficult endpoint for first-line trials in metastatic RCC."

Finally, Hotte et al.[ii], 2011 have recently examined the issues surrounding the use of PFS as a clinical trial endpoint for RCC. Their work further corroborates the position of the clinical guidance report from pCODR.

Taken in this context, GSK believes that Pazopanib represents a cost-effective therapy and should be recommended as a first-line treatment option by pCODR for patients with advanced RCC.

As a result, GSK agrees in part with the initial recommendation which recommends (limited) funding for pazopanib, because it:

- Will limit physician and patient choice as all 1st line good performance status mRCC patients will be forced to start on sunitinib, and
- Will minimize potential cost savings that could be achieved by provincial drug plans/cancer agencies (QC and Newfoundland and Labrador do not have mechanism for confidential pricing agreements and both have Sutent listed at the list price in public documents) by making sunitinib the required 1st choice 1st line mRCC treatment in good performance status patients
- Appears to be based on an assumption that the uncertainty regarding effectiveness, safety and cost-effectiveness for pazopanib compared with sunitinib are mostly not in favour of pazopanib.

[i] *Heng DY, Xie W, Bjarnason GA, Vaishampayan U, Tan MH, Knox J, et al. Progression-free survival as a predictor of overall survival in metastatic renal cell carcinoma treated with contemporary targeted therapy. Cancer. 2011 Jun 15;117(12):2637-42.*

[ii] *S.J. Hotte, G.A. Bjarnason, D.Y.C. Heng, M.A.S. Jewett, A. Kapoor, C. Kollmannsberger, J. Maroun, L.A. Mayhew, S. North, M.N. Reaume, J.D. Ruether, D. Soulieres, P.M. Venner, E.W. Winquist, L. Wood, J.H.E. Yong, F. Saad. Progression-free survival as a clinical trial endpoint in advanced renal cell carcinoma. Current Oncology. 2011. V. 18, Supplement 2, S11-S19*

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

__X__	Support conversion to final recommendation.	____	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
2	**Summary of pERC Deliberation**	Paragraph 2, line 8	*"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."* From these two sentences it was not clear how pERC evaluated the uncertainty around the PFS or OS estimates and which of the two lead pERC to the conclusion in this section. GSK suspects that pERC was primarily concerned with the uncertainty around variance of the OS estimate for pazopanib vs. sunitinib. As a results, we have provided comments accordingly above in section 3.1 part a. Given the debate in RCC and oncology in general around OS vs. PFS endpoints of clinical trials it would helpful if pERC can clarify concerns related to the effectiveness of a product in terms of PFS and OS.

Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Note: No additional comments were submitted to pCODR by GlaxoSmithKline Inc.

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.