PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Pazopanib hydrochloride (Votrient) Resubmission for metastatic renal cell carcinoma

August 29, 2013

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Votrient (pazopanib hydrochloride– Metastatitc Renal Cell Carcinoma
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	GlaxoSmithKline

3.1 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

GSK, the manufacturer, agrees in part with the pan-Canadian Oncology Drug Review Expert Review Committee's initial recommendation regarding pazopanib. However, GSK would like to address and clarify the following issues which impact both the clinical and economic evaluations of pCODR's review:

POINT 1: The current recommendation wording, which states that pERC recommends funding pazopanib for RCC patients as an 'alternative treatment option to sunitinib', may lead to uncertainty and confusion amongst provinces, physicians and patients as to the intent of the recommendation.

The manufacturer requests that pERC simplify the recommendation statement to *"..funding pazopanib hydrochloride (Votrient) for patients with advanced or metastatic clear cell renal carcinoma as a first-line treatment option for patients with good performance status".* One potential interpretation of the current wording is that stakeholders, including provinces, physicians, and patients, may view the wording as "an alternative option *after* Sutent", which we understand is not the intent of the pERC, as this would place pazopanib outside of its indication (ie: off-label). It is the understanding of the manufacturer that the intent of the pERC recommendation is to indicate that pazopanib has therapeutic value for patients and is a valid and appropriate choice as a first-line treatment for aRCC. Therefore, the proposed recommendation would be clear, aligned with the approved indication of pazopanib in aRCC and would remove any ambiguity as to pERC's intent. Such a revision would confirm that pazopanib is a true first-line option for aRCC patients.

POINT 2: pERC expresses concern with the use of ITT as a primary end point in COMPARZ and perceives inconsistency between the intent to treat (ITT) analysis and per protocol (PP) analysis.

We ask pCODR to reconsider their assessment regarding the appropriateness of the ITT population for the primary analysis as well as their assessments regarding the consistency between ITT and PP analyses. Importantly, the ITT population is an accepted population to assess non-inferiority. Moreover, consistency has been demonstrated between ITT and PP populations through a PP sensitivity analysis, as demonstrated by the similar HRs and overlapping 95% CIs between these two populations. This approach is supported through literature and regulatory guidance on non-inferiority trials[1-3]. Please note the following points:

ITT is an accepted and valid population to assess non-inferiority:

- The ITT population is the most common primary analysis population in non-inferiority trials in oncology[1].
- The PP analysis in COMPARZ was not powered nor required to determine non-inferiority based on the defined margin of the confidence intervals (CIs). To adequately power this trial for a PP population would have required many more subjects and possibly more time thus unnecessarily delaying the availability of this data.
- Regulatory guidance on non-inferiority trials does not require the PP population analysis to be the primary or co-primary endpoint but requires consistency between analysis populations to demonstrate that trial results are sufficiently insensitive to an alternate set of subjects. Notably, the COMPARZ study, which was a European post-approval commitment trial, was reviewed by the European regulatory agency (EMA) prior to study initiation, and the manufacturer specifically inquired about the appropriateness of the ITT population for the primary analysis, to which the agency had no objection. As such, the PP analysis was conducted as part of a sensitivity analysis only, in order to establish consistency of the point estimate of the PP population to that of the overall ITT population.
- The ITT population contains all subjects, whereas no standardized definition exists for PP populations on who to exclude thus introducing potential bias. Furthermore, a PP analysis excludes major protocol deviators and therefore, as compared to the ITT analysis, expectedly contains fewer subjects available for analysis. As such, the PP population may be viewed as less representative of the real-world.

Consistency was demonstrated between the COMPARZ ITT and PP analysis populations.

- Consistency was demonstrated in COMPARZ by comparability of the HR point estimates between the ITT and PP analysis populations (Table 1). The PP population had approximately 10% fewer patients than the ITT population resulting in an expectedly wider CI. However, the HRs obtained from both analyses are similar and the CIs substantially overlap (Table 1). Moreover, the results obtained from the PP sensitivity analysis are consistent with the primary ITT analysis (CSR pg 53). As such, ITT and PP results are consistent and support the conclusion that pazopanib is non-inferior to sunitinib.

PFS (IRC-assessed, ITT) – primary analysis (CSR: pg 48)		
	Pazopanib (N=557)	**Sunitinib (N=553)**
HR (95% CI)	**1.0466 (0.8982 – 1.2195)**	
PFS (IRC-assessed, PP) – sensitivity analysis (CSR: pg 53)		
	Pazopanib (N=501)	**Sunitinib (N=494)**
HR (95% CI)	**1.069 (0.910 – 1.255)**	

POINT 3: pERC had difficulties interpreting HRQoL questionnaires in COMPARZ and PISCES due to methodological challenges.

The manufacturer requests that pERC re-consider the validity of the HRQoL questionnaires based on the following points which are provided to help clarify the HRQoL methods and instruments. Reconsideration of their value in understanding the product differences and preferences would help guide provinces, physicians and patients in choosing the most appropriate therapy option for their circumstance. The validity of these results also impact the assumptions made by the economic guidance panel regarding the health economic evaluation.

COMPARZ:

- COMPARZ assessed HRQoL with 4 validated questionnaires. The FACIT-F, FKSI-19', and CTSQ' were validated via psychometric analyses before study start'[4-9]; the SQLQ was validated post-study analysis'[10].
- There is no perfect time to assess QoL given the differences in dosing schedules of the two agents (continuous vs intermittent). For example, in COMPARZ, conducting assessments at day 28 could potentially bias against sunitinib and in favour of the pazopanib arm, whereas assessments conducted at day 42 could potentially bias the other way.
- The day 28 QoL assessment schedule in COMPARZ (through to cycle 9) was chosen to allow for comparison when patients in *both* treatment arms were on active therapy. Moreover, the CTSQ and SQLQ both ask questions about the patient's experiences over the *last 4 weeks*; assessing QoL on day 28 of a cycle allows for capturing of this recall period.

PISCES:

- As PISCES had a novel study design, there were no previously validated preference instruments available by which to assess the primary endpoint of patient preference in advanced RCC (aRCC).
- PISCES assessed HRQoL using 3 validated questionnaires. The FACIT-F and EQ-5D instruments were validated prior to study conduct; the SQLQ was subsequently validated.'[4-6,10-12] The patient preference questionnaire development was led by professor David Cella at Northwestern University in Chicago with input from leading RCC practitioners, experts in HRQoL, and was reviewed and revised based on input from patients with aRCC.
- The FACIT-F and SQLQ questionnaires (also used in COMPARZ) were completed every two weeks in PISCES, a schedule that more appropriately captures the impact of the 4/2 sunitinib dosing regimens.
- Importantly, the very similar treatment differences observed in the PISCES and COMPARZ HRQoL data suggest that the impact of the timing of HRQoL assessments in COMPARZ is likely to be minor.

  Overall, these validated instruments are capturing information about the patient experience that is important and relevant for consideration by pCODR's clinical and economic panels.

POINT 4: pERC expressed methodological concerns with inclusion of patients from the Asian study (VEG113078) in COMPARZ.

The manufacturer requests that pCODR consider the following points related to the rationale behind the inclusion of patients from the VEG113078 study into the COMPARZ trial:

- It was originally estimated that a sample size of 876 patients would be required to observe 631 PFS events by the blinded independent review committee (IRC) to provide 80% power. However, this was underestimated due to two key factors: 1) higher than anticipated rates of attrition and 2) discordance rates between IRC and investigator assessments. The 927 patients enrolled in COMPARZ were only sufficient to observe 578 events at the time of the conducted analysis, with fewer subjects in follow-up than would be necessary to reach 631 events.
- VEG113078 began enrollment when COMPARZ ended enrollment and was planned to recruit the same number of subjects that was estimated to be needed to observe the required 631 IRC-assessed PFS events (183 patients were enrolled in the VEG113078 study).
- Given the importance of providing this data for patients and the medical community in a timely manner, the decision was taken *prospectively* to combine the two study populations in order to meet the required 631 PFS events per IRC. Both study designs were identical with the exception of the collection of the coagulation parameters and that VEG113048 had no HRQoL questionnaires. All but two of the subjects in VEG113078 were enrolled to sites who participated in VEG108844.
- Importantly, the original study population was not analyzed prior to combining the two study populations and the IRC remained blinded to treatment until the end of both trials.

Overall, the addition of VEG113078 to COMPARZ was methodologically sound.

POINT 5: pERC states 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).*" This statement may lead to the assumption by payers that drug costs due to dose modifications would be lower for sunitinib.

- The manufacturer suggests removing the reference to sunitinib, as dose modification may occur with either drug and dose modifications are not exclusive to sunitinib in clinical practice.

ISSUE 6: The manufacturer disagrees with the Economic Guidance Panel's statement that "A *significant part of this gain is from over-estimating PFS gain, which arises when survival and progression are modeled independently in the partition-survival methodology, which the CGP considered as inappropriate.*" (EGR pg 5).

- To calculate QALYs for pazopanib and sunitinib, the empirical (i.e., Kaplan Meier) survival distributions, for both PFS and OS for both arms of the COMPARZ trial, were used. The major part of the difference in QALYs of pazopanib vs. sunitinib is due to a better utility during PFS and longer PPS for pazopanib. This increase in QALYs is offset by a decline of QALYs due to shorter PFS for pazopanib. Of the total gain in QALYs, 63% is due to better utility during PFS and 37% is due to longer PPS.
- The manufacturer suggests the following modified wording: "A *major part of this gain is due to a better utility during PFS stage and the remainder is due to the longer estimated PPS with pazopanib vs. sunitinib, which is a consequence of estimating PFS and OS, independently based on the empirical (Kaplan Meier) survival distributions for PFS and OS.*"

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.

_____ Support conversion to final recommendation.	__X__ 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
			See comments above.

3.2 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.

Please note that new evidence will be 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 providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
			See comments above.

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

[1] **pCODR Initial Recommendation document: pg 6**

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.