pan-Canadian Oncology Drug Review

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

Pazopanib (Votrient) for Soft Tissue Sarcoma

November 29, 2012

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

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3. Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Votrient (pazopanib) for advanced soft tissue sarcoma
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	GlaxoSmithKline Inc.

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 ____ agrees in part __X__ Disagree

GSK disagrees with the initial recommendation for the following 4 reasons:

1. **"There is an overall clinical benefit to pazopanib in the treatment of advanced and metastatic STS, based on data from a high quality randomized trial (PALETTE) that demonstrated a clinically and statistically significant 3-month improvement in median PFS for patients receiving pazopanib compared to placebo**." (Initial Clinical Guidance Report, Conclusions p.3 paragraph 1)

   - "The median PFS of 4.6 months in patients receiving pazopanib, and 3 month improvement compared with placebo, should be viewed in the context of the limited efficacy of second-line therapies in STS. For example, in the only randomized placebo-controlled study in this setting, ridaforolimus administered as maintenance therapy produced a statistically significant improvement in PFS (HR 0.72, p=0.0001), but the difference in median PFS was only 3.1 weeks (17.7 versus 14.6 weeks). Similarly, in two randomized phase II trials comparing combination docetaxel/gemcitabine with gemcitabine alone, median PFS for the combination therapy ranged from 4.2-6.3 months, and improvements compared with single agent therapy ranged from 1.2-2.5 months."[1]
   - The benefit of pazopanib treatment over placebo was consistent across multiple STS subtypes, and regardless of the number of previous lines of therapy.
   - The PFS gain (3 months incremental; 4.6 months absolute) is significant in a disease where the median survival is estimated to be 12 month from diagnosis of metastatic disease and 8 months for 2nd line chemotherapy.[2] This represents a clear, meaningful clinical benefit for STS patients.

2. **"Although there was only a small 1.8 month non-significant improvement in OS, this is consistent with data from several randomized trials evaluating standard palliative chemotherapy for STS**.´ (Clinical Guidance Report, Conclusions p.3 paragraph 2, first bullet)

   - Even agents such as doxorubicin and ifosfamide that are accepted as standard of care in advanced STS have not shown improvement in OS.[3] "In a meta-analysis comparing single agent doxorubicin to doxorubicin-based combination chemotherapy, there was no

significant improvement in OS for combination chemotherapy, despite higher response rates and better PFS in most studies."[3]

- PFS benefit provides clinical value for advanced STS patients. OS was numerically (10.7 months vs. 12.6 months) but not statistically significantly higher than in the placebo arm, but was likely confounded by an imbalance in post-study therapies.

3. **"Important patient concerns exist with currently available chemotherapies and are addressed by the convenient oral administration and relatively mild toxicities associated with pazopanib therapy."** (Initial Clinical Guidance Report, Conclusions p.3 paragraph 2, fifth bullet)

   - Pazopanib is an oral agent, convenient to administer, with mild toxicity compared to standard drugs (doxorubicin, ifosfamide) given as palliative chemotherapy for STS. Furthermore, pazopanib is an important option for patients who are deemed unfit for chemotherapy.
   - While the PALETTE study did not report statistically significant differences in quality of life for Votrient vs. placebo, patients in the Votrient arm received an active agent with known toxicities and did not report lower quality of life vs. patients receiving placebo.

4. **Although pazopanib was not cost effective for the treatment of STS compared to treatment with placebo, the budget impact is minimal.**

   - Although pazopanib is not cost-effective compared to placebo for the treatment of advanced or metastatic Soft Tissue Sarcoma, consideration should be given to the minimal budget impact that would be associated with pazopanib's use for STS and also the likelihood that oncologist will continue to use IV chemotherapy agents which have poor evidence to support their use and as the first novel treatment option for patients with this condition in over 30 years would have.
     - Pazopanib is approved for the treatment of STS following prior chemotherapy. The estimated total number of refractory STS patients was 430 in Canada in 2008. Of these patients, many will be ineligible for pazopanib treatment due to age or comorbidities, 20% of patients will be ineligible due to having liposarcoma, therefore a reasonable estimate for eligible patients is 150-320/year across Canada.
     - Comparison of pazopanib to placebo for the purpose of the clinical safety and efficacy is appropriate; however, most of the time oncologists will continue to treat patients with many rounds of non-oral chemotherapies, each of which is associated with both cost and adverse events. These trade-off decisions are not easily captured and were therefore not included in the modeling due to lack of head-to-head and an adjusted indirect treatment comparison.

References:

1. Pan-Canadian Oncology Drug Review Clinical Guidance Report Pazopanib, Limitations of Evidence p.9, second bullet).
2. Clinical Efficacy and Safety Summary, Votrient for Soft Tissue Sarcoma, Executive Summary, p4)
3. Pan-Canadian Oncology Drug Review Clinical Guidance Report Pazopanib, Limitations of Evidence p.9, third bullet).

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.

Recommendation does not require reconsideration by pERC.

__X__ Do not support conversion to final recommendation.

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

3.2 Comments Related to Submitter or Manufacturer-Provided Information

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

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

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.