PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Ruxolitinib (Jakavi) for Polycythemia Vera

March 3, 2016

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	**Ruxolitinib (Jakavi®). The control of hematocrit in adult patients with polycythemia vera (PV) resistant to or intolerant of a cytoreductive agent.**
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Novartis Pharmaceuticals

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:

__x_ Agrees ____ agrees in part ____ disagree

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.
Recommendation does not require reconsideration by pERC.

___ 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
1	pERC recommendation	1st paragraph	"Funding should be for the treatment of patients with polycythemia vera who have disease resistant to hydroxyurea (HU) or who are intolerant of HU and have a good performance status." For consistency with the Product Monograph, we suggest to have the following reimbursement criteria: "Funding should be for the treatment of patients with polycythemia vera who have disease resistant to a *cytoreductive agent* or who are intolerant of a *cytoreductive agent*."

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
4	SUMMARY OF PERC RECOMMENDATION	5th paragraph	"pERC also noted that a previous review's recommendation of ruxolitinib in the treatment of myelofibrosis suggested monitoring no later than 24 weeks after starting ruxolitinib. pERC felt this observation period was also appropriate for PV and that this allowed for consistency across indications." Although the primary endpoint in COMFORT I (phase III trial in myelofibrosis) was after 24 weeks of follow-up, the one in RESPONSE (phase III trial in PV) was after 32 weeks of follow-up. Monitoring after 32 weeks of treatment is also consistent with the economic evaluation modeling submitted and used by pERC to establish the ruxolitinib recommendation for reimbursement. Therefore, Novartis suggests monitoring at week 32 for this indication in polycythemia vera instead of 24 weeks.
7	EVIDENCE IN BRIEF (OVERALL CLINICAL BENEFIT)	Need: No curative treatment for patients with PV	"The treatments currently used (...) are either marginally effective..." Suggested edit: "Although there are no approved treatments for polycythemia vera, those typically used by physicians are either marginally effective..."
9	COST-EFFECTIVENESS ESTIMATES: HIGH COST OF RUXOLITINIB A KEY DRIVER	2nd paragraph	Pertaining to the assumption: same utility for treatment arms. Feedback received from the clinical guidance panel and the patient advocacy group strongly support that patients treated with ruxolitinib have improved quality of life compared with patients treated with standard therapies. With such compelling evidence, the improvement of QoL with ruxolitinib observed in the clinical trial should translate into a difference in utilities vs. BAT. An analysis in which the utility is the same for ruxolitinib and BAT would only be appropriate if the treatment was not expected to

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			improve quality of life. Data from the RESPONSE and RESPONSE-2 trials do not support this assumption. Furthermore, a mapping exercise was required to generate utilities from the RESPONSE trial QoL data for use in the model. Recently released data (figure-1) from the RESPONSE-2 trial comparing ruxolitinib to BAT in PV patients who are resistant or intolerant to HU support the validity of the magnitude of the utility difference used in the model (Novartis Oncology RESPONSE 2; CSR CINC424B2401). The EQ-5D instrument used in this trial generated direct utilities (no need for mapping) for the two trial arms. Ruxolitinib resulted in 0.05 (0.77 baseline vs. 0.82 week28) utility improvement from baseline whereas BAT resulted in a decrement of -0.03 (0.79 baseline vs. 0.76 week28) from baseline. This gain of 0.08 in utility in favor of ruxolitinib vs. HU is in line with the magnitude of the utility difference used in the model (0.11). Figure-1: EQ-5D utility data from RESPONSE2 trial Ruxolitinib (61 patients) *Baseline* *WEEK 28* 0.77 0.82 BAT (23 patients) Baseline WEEK28 0.79 0.76 Restoring a difference in the on-treatment utility but Taking into account all the other EGP assumptions resulted in an ICER of $196,076/QALY. In summary, given these compelling data consideration should be given not to make the proposed assumption: same utility for treatment arms (0.775)".

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.cadth.ca/pcodr 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.cadth.ca/pcodr 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.cadth.ca/pcodr 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.