pan-Canadian Oncology Drug Review

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

Ruxolitinib (Jakavi) for Myelofibrosis

January 14, 2013

3 Feedback on pERC Initial Recommendation

Name of the drug indication(s):	Ruxolitinib (Jakavi) for myelofibrosis
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback:	Novartis Pharmaceuticals Canada 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 _x_ agrees in part ____ disagree

Novartis, the Manufacturer of the drug under review, agrees in part with the initial recommendation.

RECOMMENDATION (pg1): *"Ruxolitinib should be funded in patients with intermediate-2 to high risk symptomatic myelofibrosis,…"*

We would like to clarify that prognostic risk assessment scores such as the IPSS help predict median survival and assist in deciding whether a patient is a suitable candidate for allogeneic stem cell transplant (alloSCT), the only existing cure for MF. However, for several reasons these scores do not serve to identify an appropriate therapy for patients with MF.

Firstly, regardless of risk assessment categorization, all individuals with MF may experience splenomegaly and an array of disabling disease-associated symptoms. As the severity of the disease-associated symptoms of MF does not necessarily correlate with patient prognosis, patients in lower-risk categories may still endure a considerable symptom burden that could be improved with treatment.

Secondly, IPSS risk category is typically determined at the time of patient diagnosis. As patients with MF may live for many years and their disease is likely to progress, their actual risk may change over time. However, this change may not be formally assessed and patients who have progressed may remain ineligible for a risk category-indicated treatment, if the IPSS were to be strictly applied.

The need to address splenomegaly and disease-related symptoms exists across all IPSS risk categories, from low- to high-risk patients. As ruxolitinib is the only treatment indicated to treat these symptoms, this therapy addresses a critical unmet medical need for all patients with MF.

SUMMARY OF pERC DELIBERATIONS (pg3 pa2): *"...budget impact of a number of issues relating to dosing:… drug wastage around dose adjustments..."*

Drug wastage resulting from dose adjustments can be avoided or at least minimized because the dose adjustment schedule is clearly outlined in the Product Monograph and physicians can adjust prescription periods accordingly. For example, the Product Monograph states that the starting dose should not be increased in the first 4 weeks.

Consequently, the first prescriptions should cover one month of treatment only. Thereafter, complete blood count is monitored every 2-4 weeks until doses are stabilized. Because the dose is adjusted no more frequently than at 2-week intervals, monitoring visits coincide with dose adjustment visits and physicians can adjust prescription period accordingly. Once the dose is stabilized, prescription period can be extended.

SUMMARY OF pERC DELIBERATIONS (pg2, pa4): *"…there are case reports of a rebound effect upon discontinuation of ruxolitinib (Teferi 2012), although this was not observed in either the COMFORT I or COMFORT II studies."*

Rebound after ruxolitinib discontinuation was described at one center alone and was not reported by other investigators in any other study (i.e. approximately 170 centers).

Initial Economic Guidance Report (pg2 pa5): *"… Economic Guidance Panel reanalyses that assumed the model's time horizon to be shorter than the proposed lifetime time horizon modelled by the manufacturer…"*

We acknowledge the uncertainty that can be raised in extrapolations. Following CADTH HTA guidelines, extrapolation until death is recommended in order to capture all costs and benefits associated (CADTH HTA guidelines, 2006). In addition, at 144 weeks the majority of patients are still alive as such the time horizon should be beyond the Economic Guidance Panel's adjusted time horizon (144 weeks). In regards to clinical data availability, adjustment to a 144-week time horizon is limiting, as correctly highlighted in the clinical follow-up data. Even if the model uses the most conservative approach, assuming no overall survival benefit (reviewer's assumption), the patients on JAKAVI continue to benefit from the improved QoL. Finally, the current appraisal appears to be inconsistent with previous modeling assessments, whereby extrapolation and re-adjustment to align with clinical data was not termed as a major concern.

We urge the pERC to reconsider the above points, mainly the assumption regarding the shorter time horizon which is inconsistent with CADTH HTA guidelines and with previous pCODR appraisals.

Initial Economic Guidance Report (pg4 pa2): *"…the manufacturer assumed that ruxolitinib had a survival benefit based on an observational study that compared ruxolitinib patients to a historical cohort…"*

The model uses Health State- specific Survival Hazard Ratios and not drug-specific Survival Hazard Ratios. Both treatments could demonstrate survival benefit if they achieve a 50% or greater reduction in palpable spleen length. Indeed, because the model considered different health states categorized by levels of spleen-volume reduction achieved, it was considered more appropriate to differentiate survival based on these differences in spleen-size reduction rather than simply on the treatment the MF patients received. Therefore, the study by Verstovsek and colleagues comparing the survival differences among patients achieving different levels of spleen-size reduction over a median follow-up of 32 months was used in the model (Verstovsek et al., 2011).

Initial Economic Guidance Report (pg1 pa4): *"…The model has not considered whether ruxolitinib will enable patients to spend more time working or with family…"*

As stated by the reviewer, the model adopts the perspective of the publicly funded health care system which is appropriate for pCODR because drug funding

recommendations must be considered from a health system perspective. However, a separate analysis assessed the cost-effectiveness of JAKAVI from a societal perspective. The model included assumptions with regards to indirect costs in terms of loss of productivity due to the impact of MF. The results showed that due to the higher number of hours of work lost by MF patients and their carers for BAT patients, the indirect costs associated with these patients were higher than the indirect costs of JAKAVI patients. This resulted in ICERs ranging from $62,000 to $80,000/QALY.

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
5	EVIDENCE IN BRIEF (OVERALL CLINICAL BENEFIT)	Pa 4, Ln 24	*"The standard treatments currently used are either marginally effective…"* Suggested edit: *"Although there are no approved treatments for myelofibrosis, those typically used by physicians are either marginally effective…"*
7	ADOPTION FEASIBILITY	Pa1, Ln6	*"…some patients being treated in the community for myelofibrosis may need to be treated in cancer treatment centres to allow for appropriate monitoring of ruxolitinib, which would increase workload in these clinics."* Based on Novartis experience with the Special Access Program, patients can be treated in the community.

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.