pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Ruxolitinib (Jakavi)

Submitted Funding Request:
For the treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea

Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: November 24, 2015	**Submission Date:** August 27, 2015
Initial Recommendation: January 8, 2016	**Final Recommendation:** March 3, 2016

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding ruxolitinib (Jakavi) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with polycythemia vera who have disease resistant to hydroxyurea (HU) or who are intolerant of HU according to the modified European LeukemiaNet Criteria used in the RESPONSE trial (specific criteria listed below) and have a good performance status. Treatment should continue until unacceptable toxicity or disease progression.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of ruxolitinib compared with standard therapy, based on observed response rates of both hematocrit control and reduced spleen size, as well as a reduction in polycythemia vera symptoms and improved quality of life. While pERC was confident there is a net clinical benefit with ruxolitinib, the Committee was uncertain of the magnitude of benefit when compared with standard therapy due to limitations in the evidence from available clinical trials. Additionally, pERC was unable to determine how ruxolitinib compares with standard therapy with regard to longer-term outcomes, such as, overall survival and thrombosis-free survival.

pERC also noted that ruxolitinib aligned with patient values, as there is a need for more effective treatment options for patients with polycythemia vera who have disease resistant to or intolerant of hydroxyurea.

The Committee concluded that at the submitted price and based on the Economic Guidance Panel`s best estimate, ruxolitinib was not cost-effective compared with standard therapy in this population.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit of ruxolitinib for the treatment of patients with polycythemia vera who have disease resistance to or intolerance of hydroxyurea, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness to an acceptable level.

Managing Monthly Drug Costs to Improve Cost-Effectiveness
In addition to the above, and given the high incremental cost of ruxolitinib, jurisdictions may want to consider implementing measures to manage the monthly cost of ruxolitinib, which could help to improve cost-effectiveness to an acceptable level. These measures could include the following:

- monitoring for a response to treatment no later than 24 weeks after starting ruxolitinib
- ongoing monitoring for response as treatment duration may be indefinite
- tapering ruxolitinib dose when considering discontinuation because of the possible rebound effects
- considering the impact of dose adjustments on tablet burden since ruxolitinib is flat priced per tablet, not per milligram and actual use in clinical practice may significantly increase costs, depending on what combination of tablets is used
- stopping criteria based on disease progression.

Developing Guidelines on Appropriate Definition of Progression for Treatment Discontinuation with Tumour Groups
pERC noted that evidence was not available to indicate an optimal duration of treatment with ruxolitinib and use may be indefinite if patients continue to respond. pERC considered that the definition of progression and guidance on discontinuation of treatment used in the pivotal trial for ruxolitinib may not reflect common clinical practice in Canada. pERC agreed that a definition for progression, based on input from provincial tumour groups, would be helpful in determining clinically reasonable parameters for response monitoring and discontinuation of treatment with ruxolitinib.

Ruxolitinib use in patients with polycythemia vera who are resistant to or intolerant of a cytoreductive agent other than hydroxyurea
pERC noted that evidence was not available to support the use of ruxolitinib in patients with polycythemia vera who are resistant to or intolerant of a cytoreductive agent other than hydroxyurea (e.g. interferon). pERC noted that the use of ruxolitinib in cases of resistance to or intolerance of other cytoreductive therapies may apply to a very small subset of patients in the Canadian setting and should be considered on a case-by-case basis with the stopping provisions as discussed above. pERC agreed that a process, based on provincial guidelines, to allow for the review and approval of individual cases by hematologists with expertise in polycythemia vera, should be made available to assess those uncommon instances.

MODIFIED EUROPEAN LEUKEMIANET CRITERIA TO DEFINE RESISTANCE TO OR INTOLERANCE OF HYDROXYUREA

Resistance to hydroxyurea (HU) was considered if after three months of at least 2 g/day of HU or at the maximally tolerated HU dose if that dose is < 2 g/day, patients showed:

- need for phlebotomy to keep HCT < 45%%, or
- uncontrolled myeloproliferation (platelet > 400 x 10^9/L and WBC > 10 x 10^9/L), or
- failure to reduce massive splenomegaly > 50% as measured by palpation.

Intolerance of HU was considered after any dose of HU, if patients showed:

- absolute neutrophil count < 1.0 x 10^9/L, or platelet < 100 x 10^9/L or hemoglobin < 100 g/L at the lowest dose of HU required to achieve a response (response defined as HCT < 45% without phlebotomy, and/or all of the following: platelet ≤ 400 x 10^9/L, WBC ≤ 10 x 10^9/L, and non-palpable spleen), or
- presence of leg ulcers or other unacceptable HU-related non-hematological toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever, defined as Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade 3 or 4, or more than one week of CTCAE version 3.0 grade 2, or permanent discontinuation of HU, or interruption of HU until toxicity resolved, or hospitalization due to HU toxicity).

SUMMARY OF pERC DELIBERATIONS

Polycythemia vera (PV) is an uncommon, chronic progressive myeloproliferative neoplasm that is characterized primarily by an elevation of red blood cells. However, despite being uncommon, the survival of patients with PV on current treatment is 13 years or greater and there is a potentially large prevalent population of patients with PV. Since treatment can continue for many years, over time many patients will develop disease resistance to or intolerance of hydroxyurea (HU). The goals of treatment are to alleviate PV-related symptoms and to decrease the risk of thrombosis events and progression to hematological complications (e.g., myelofibrosis or acute myeloid leukemia). Currently, there is no standard of care for the treatment of PV; treatments include HU, phlebotomy, interferon, busulfan, anagrelide, lifestyle modifications, and best supportive care. These treatment options have limited effectiveness and are associated with substantial toxicities, therefore pERC considered that there is an unmet need for effective therapies for patients with PV who have disease resistant to or intolerant of HU.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one ongoing, open-label, randomized phase III trial (RESPONSE) evaluating ruxolitinib compared with best available therapy (BAT) in patients with PV resistant to or intolerant of HU. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that these comparisons were appropriate and reflective of standard therapy options for PV in the Canadian setting. pERC felt the modified European LeukemiaNet (ELN) criteria used in the RESPONSE trial to define resistance to or intolerance of HU were reasonable. In deliberating on the results of the RESPONSE trial, pERC noted that the majority of patients in the BAT group crossed-over to the ruxolitinib group. As a result, there was a lack of comparative data on long-term outcomes with ruxolitinib therapy in PV such as overall survival (OS). Upon reconsideration of the pERC Initial Recommendation, pERC acknowledged feedback from the Provincial Advisory Group (PAG) regarding the lack of survival data. pERC reiterated that a trial incorporating robust long-term outcomes such as OS would likely not be undertaken because of the long natural history of this disease and because equipoise no longer exists. Therefore, pERC was unable to determine if there is an OS advantage for ruxolitinib.

pERC noted that a significantly higher proportion of patients on ruxolitinib achieved the primary outcome of the trial, a composite response of both hematocrit control and ≥ 35% reduction in spleen volume. Irrespective of achieving response, the majority of patients in the ruxolitinib group continued on treatment. pERC discussed that the duration of treatment with ruxolitinib may be indefinite. pERC also carefully considered symptom reduction and quality of life (QoL) results from the RESPONSE trial. Three scales were used to measure symptom reduction: a modified version of the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) patient diary, Pruritus Symptom Impact Scale, and the Patient Global Impression of Change (PGIC). QoL was measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), a validated cancer-specific QoL scale used in multiple different tumour sites. A significantly higher proportion of patients on ruxolitinib compared with those on BAT achieved a 50% reduction in total symptom score. pERC noted that similar results were seen in individual symptoms including itching, night sweats, and abdominal discomfort. Symptom reduction results for the Pruritus Symptom Impact Scale and PGIC also favoured ruxolitinib. pERC noted that from baseline to week 32, QoL significantly improved in the ruxolitinib group and did not for the BAT group. The open-label design of the trial made the interpretation of the magnitude of improvements reported difficult because investigators and patients may have been biased to report more favourably for the ruxolitinib group. Furthermore, some of the scales used to measure patient-reported outcomes in the trial have not been validated for the PV setting. However, pERC acknowledged and appreciated the efforts undertaken in the RESPONSE trial to collect clinically meaningful data on specific symptoms relevant to patients with PV (e.g., pruritus, cognitive impairment) and QoL. pERC also noted blinding of patients may not have been feasible in this treatment setting because patients would be familiar with the side effect profile of HU. Overall, pERC noted that these outcomes were highly valued by patients due to their impact on daily functioning; pERC also noted that

the results observed in the RESPONSE trial aligned with patients' direct experiences, as reported in the patient advocacy group input.

pERC discussed the toxicity profile of ruxolitinib and noted that the incidence of adverse events was similar between the ruxolitinib and BAT groups. The proportion of patients with overall grade 3 or 4 adverse events was slightly higher in the ruxolitinib group compared with the BAT group, with the exception of the proportion of thrombotic events, which was slightly lower in the ruxolitinib group. However, no statistical comparisons of the differences in adverse event rates between groups were performed. It was also noted that in the RESPONSE trial the most common adverse events observed with ruxolitinib were hematologic. pERC considered that these treatment-related toxicities are manageable adverse events commonly observed in patients with hematological malignancies. Patients in the ruxolitinib and BAT groups had similar low rates of progression to myelofibrosis or acute myeloid leukemia within 80 weeks of follow-up.

Differing opinions were expressed by pERC members regarding the interpretation of the results from the RESPONSE trial favouring ruxolitinib given the many limitations of the design of the trial. However, the majority of pERC members felt that there was a net clinical benefit with ruxolitinib compared to standard therapy for patients with PV that is resistant to or intolerant of HU. Overall, the Committee was uncertain of the magnitude of benefit of ruxolitinib compared with standard therapies. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from PAG regarding the small benefits based on observed response rates of hematocrit control, reduced spleen size, and reduction in symptoms, when balanced against the very high cost of this treatment. pERC relies on the deliberative framework to guide decision making and reiterated that in the context of this drug and disease, the Committee felt that there was a net clinical benefit with ruxolitinib compared to standard therapy for patients with PV that is resistant to or intolerant of HU.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter regarding consistency of the pERC Initial Recommendation compared with the Health Canada Product Monograph; ruxolitinib has a Health Canada approval for the control of the hematocrit in adult patients with polycythemia vera resistant to or intolerant of a cytoreductive agent. pERC acknowledged and agreed with the CGP that cases of resistance to or intolerance of other cytoreductive therapies (e.g., interferon) may apply to a very small subset of patients in Canadian clinical practice and the use of ruxolitinib should be considered on a case-by-case basis.

pERC deliberated on patient advocacy group input. It was noted that the robust number of patients who had direct experience with ruxolitinib was very useful to pERC in determining whether use of ruxolitinib for the treatment of patients with polycythemia vera resistant to or intolerant of HU aligned with patient values. Overall, patients with PV valued access to therapies that provide blood count control, symptom relief, improved QoL, and an alternative toxicity profile. Patients also reported that their tolerance for side effects is higher for treatments that delay progression or reduce the need for regular phlebotomy. Patients reported that hematocrit control had a significant impact on concentration levels and overall day-to-day QoL. pERC discussed that the patient advocacy group expressed a desire for use of ruxolitinib for patients who do not have disease resistance to or intolerance of HU or who do not have disease progression on HU. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group regarding limited access to ruxolitinib based on criteria of resistance to or intolerance of hydroxyurea. pERC reiterated that funding recommendations need to be evidence-informed, and at this time, there is currently no evidence to support or refute a recommendation for treatment with ruxolitinib in patients with PV who do not have disease resistance to or intolerance of HU or in the first-line setting. pERC concluded that ruxolitinib for the treatment of patients with polycythemia vera resistant to or intolerant of HU aligned with patient values.

pERC deliberated on the cost-effectiveness of ruxolitinib. Survival data were not captured in the RESPONSE trial; therefore pERC noted that there was a high level of uncertainty in the clinical inputs used in the economic evaluation. Upon reconsideration of the pERC Initial recommendation, pERC acknowledged that the pCODR Economic Guidance Panel (EGP) modified their reanalysis to acknowledge feedback from the submitter regarding the use of equal utility values for both the ruxolitinib and best available therapy groups. Despite this modification, pERC concluded that the EGP's estimated range for incremental cost-effectiveness ratios was likely more realistic than the submitter's estimates and ruxolitinib could not be considered cost-effective. Furthermore, the high incremental cost associated with ruxolitinib was a key cost driver of the incremental cost-effectiveness ratios. pERC also discussed that there was uncertainty in the estimates of incremental cost due to:

- flat per tablet pricing structure of ruxolitinib and possible dose adjustments that may require multiple strengths of tablets
- need for ongoing monitoring to ensure patients are responding to ruxolitinib
- indefinite duration of treatment for patients
- dose tapering that is required upon discontinuation of ruxolitinib

Therefore, pERC considered that there was considerable uncertainty in the cost-effectiveness estimates provided for ruxolitinib.

pERC discussed factors that could impact the feasibility of implementing a recommendation for ruxolitinib. The Committee noted that PV is an uncommon condition; therefore the burden of illness is likely small in terms of the incident population. However, because this disease has a long natural history and there are currently only marginally effective treatments, there may be a large prevalent population of patients in the community who will require treatment with ruxolitinib. pERC also noted that to enhance feasibility and manage the monthly drug costs associated with ruxolitinib use in actual practice, provinces may need to consider factors such as explicit monitoring plans to evaluate patients for response and the need for ongoing treatment. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from PAG regarding the definition of discontinuation criteria for treatment with ruxolitinib. pERC acknowledged that the treatment duration of ruxolitinib will be a substantial implementation issue and that there is currently no evidence to support or refute specific criteria for discontinuation. pERC noted and agreed with PAG that provincial tumour groups should work together to define an appropriate duration of treatment and assessment parameters at a national level to ensure consistency across the country. In addition, the budget impact relating to dosing of this drug must also be considered. In particular, concern was expressed regarding ruxolitinib being priced per tablet rather than per milligram, the variety of dosing schedules that may be used, drug wastage around dose adjustments, and the need for dose tapering upon discontinuation of therapy. Upon reconsideration of the pERC Initial Recommendation, pERC acknowledged the potentially large budget impact associated with ruxolitinib and that it will be a substantial barrier for implementation of a recommendation for ruxolitinib. pERC 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. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the submitter regarding monitoring no later than 24 versus 32 weeks after starting ruxolitinib. pERC reiterated that monitoring no later than 24 weeks after starting ruxolitinib was appropriate for the reasons previously stated.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group supporting the development of appropriate monitoring plans to be sure that patients on therapy are responding as desired and a recommendation that the development of appropriate guidelines should not be limited by cost-effectiveness considerations initially. As a health technology assessment body, pCODR examines the comparative effectiveness of different treatment strategies looking at multiple dimensions while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society. Consequently, cost-effectiveness along with overall clinical benefit, alignment with patient values, and feasibility of adoption into the health system, are domains of pERC's deliberative framework in making drug funding recommendations.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy groups (Canadian Myeloproliferative Neoplasms Network)
- input from pCODR's Provincial Advisory Group

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group.
- one patient advocacy group (Canadian Myeloproliferative Neoplasms Network)
- the Submitter (Novartis Pharmaceuticals Canada Inc.)

The pERC initial recommendation was to fund ruxolitinib 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.

Feedback on the pERC Initial Recommendation indicated that the Provincial Advisory Group and patient advocacy group agreed in part with the initial recommendation. The submitter agreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of ruxolitinib (Jakavi), compared with standard care options, in adult patients with polycythemia vera (PV) resistant to or intolerant of hydroxyurea (HU).

Studies included

The pCODR systematic review included one ongoing, open-label, randomized phase III trial (RESPONSE) that evaluated the efficacy and safety of ruxolitinib compared with best available therapy (BAT). The choice of BAT was at the discretion of the investigator. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that these comparisons were appropriate and reflective of standard therapy options for PV in the Canadian setting. The most common initial therapies used in the BAT group of the trial were: HU (58.9%), no anti-cancer medication (15.2%), and interferon (11.6%). All patients received low-dose Aspirin unless it was contraindicated. The trial permitted patients randomized to BAT to crossover to ruxolitinib at or after week 32, and the majority of patients in the BAT group crossed over (85.7%).

In addition to the RESPONSE trial, the pCODR review also included contextual information on the type and degree of resistance to and intolerance of HU that would be considered in order to support a switch in treatment to ruxolitinib. In addition, three additional studies were summarized; these retrospective studies were used to inform the pharmacoeconomic evaluation on elevated white blood cell (WBC) count and its association with worse overall survival (OS) in PV disease (Tefferi et al. 2013; Alvarez-Larran 2012; Bonicelli et al. 2012).

Patient populations: Patients with HU resistance or intolerance according to a modified European LeukemiaNet Criteria

A total of 222 patients with PV who had demonstrated resistance to or intolerance of HU based on the modified European LeukemiaNet (ELN) criteria were enrolled in the RESPONSE trial.

Treatment groups were generally balanced with respect to baseline characteristics and disease history indicating that randomization had worked well. The median time since diagnosis was 8.2 and 9.2 years in the ruxolitinib and BAT groups, respectively. The median duration of prior treatment with hydroxyurea was approximately three years in both groups. The majority of patients (98%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Hydroxyurea resistance was noted in 47% and 54% of

patients in the ruxolitinib and BAT groups, respectively. Hydroxyurea intolerance was noted in 46% and 55% of patients in the ruxolitinib and BAT groups, respectively.

Key efficacy results: Improved hematocrit control, spleen volume, and symptom burden

The primary end point in the RESPONSE trial was a composite response endpoint including the proportion of patients who achieved both HCT control and a reduction in spleen volume of ≥ 35%, as assessed by either magnetic resonance imaging (MRI) or computed tomography (CT) imaging, at week 32.

Other key efficacy outcomes deliberated upon by pERC were duration of primary response, complete hematological response (CHR) at 32 weeks, and symptom reduction. A higher proportion of patients in the ruxolitinib group achieved the composite response of hematocrit control and ≥ 35% reduction in spleen volume, compared with the BAT group at 32 weeks (20.9% versus 0.9%, respectively). Complete hematologic response was significantly higher in the ruxolitinib group compared to the BAT group (23.6% versus 8.9%, respectively, *P*=0.003). The primary response was maintained at 48 weeks by 19.1% and 0.9% of patients in the ruxolitinib and BAT groups, respectively. At 80 weeks, only one patient lost their response in the ruxolitinib group. pERC noted that at 80 weeks, 82.7% of patients in the ruxolitinib group and those who crossed over from the BAT group were still on treatment with ruxolitinib.

Symptom reduction was measured by three scales in the RESPONSE trial. A significantly higher proportion of patients on ruxolitinib compared with BAT achieved a 50% reduction in total symptom score (49% versus 5%, respectively). pERC noted that ruxolitinib was associated with greater reduction in all symptom clusters such as cytokine symptom cluster score and individual symptom scores relative to BAT. Symptom reduction results favouring ruxolitinib were also observed in the Pruritus Symptom Impact Scale and Patient Global Impression of Change (PGIC). pERC considered that the magnitude of these improvements was clinically meaningful and that, based on input from patient advocacy groups, these outcomes are important to patients.

Quality of life: Improvements in quality of life, consistent with patient input

Quality of life was evaluated in the RESPONSE trial using the European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire (EORTC QLQ-C30). This consists of five sub-scales on function (physical, role, emotional, cognitive, and social), a global health status and quality of life (QoL) composite score, and individual symptom subscales (e.g., fatigue, pain, nausea). pERC acknowledged and appreciated the efforts undertaken in the RESPONSE trial to collect clinically meaningful data on specific symptoms relevant to patients with PV (e.g., pruritus, cognitive impairment) and QoL.

There was a greater improvement in overall health QoL score for the ruxolitinib group compared to the BAT group from baseline to week 32 (mean change of 10.9 versus –4.9 for the ruxolitinib and BAT groups, respectively). A minimally important difference in overall health QoL score was achieved in 46% and 10% of patients treated with ruxolitinib and BAT, respectively. At 32 weeks, mean changes from baseline to week 32 were significantly improved in ruxolitinib-treated patients for the individual symptom sub-scales of fatigue, pain, and insomnia. For the same subscales, there were no significant changes for BAT-treated patients. pERC considered that these improvements in QoL were consistent with reductions in spleen volume and symptoms that were observed in the RESPONSE trial. In addition, pERC noted that improvements in QoL were very important to patients and were consistent with the detailed descriptions provided in patient advocacy group input related to patients' experiences with ruxolitinib. These patients noted that their QoL improved following ruxolitinib treatment due to reductions in their spleen size, improvements related to symptoms (itching, pain, and energy level), and reduced reliance on phlebotomies.

Safety: Low rates of grade 3 or 4 adverse events, hematologic adverse events manageable

pERC discussed the adverse events observed in the RESPONSE trial. The proportion of patients with grade 3 or 4 adverse events was slightly higher in the ruxolitinib group compared with the BAT group (32.7% versus 28.8%, respectively). Similarly, treatment-related adverse events occurred in a higher proportion of patients treated with ruxolitinib (59.1%) compared with BAT (33.3%). Compared with BAT, ruxolitinib was associated with a higher frequency of hematologic adverse events such as anemia and thrombocytopenia. BAT was associated with a higher frequency of neutropenia and lymphopenia. pERC noted that the majority of adverse events were hematologic, which are routinely encountered and managed by hematologists and oncologists when caring for patients with cancer. Non-hematological adverse events reported in the RESPONSE trial included: diarrhea, muscle spasms, dyspnea, herpes zoster infections, and pruritus. No deaths were reported in the ruxolitinib or BAT group through week 32.

Limitations: No long term overall survival data

The RESPONSE trial did not report data on OS. However, pERC noted that these analyses would likely be confounded by cross-over as the majority of patients in the BAT group switched group to receive ruxolitinib at 32 weeks. Furthermore, PV is a chronic disease with current median survival for treated patients more than 13 years. pERC noted that there are no long-term data from the RESPONSE trial to inform long-term efficacy or safety outcomes associated with treatment with ruxolitinib.

Treatment duration: Indefinite treatment length requires monitoring for response

pERC discussed that the duration of treatment with ruxolitinib is not well-defined, and is potentially indefinite if patients continue to respond to ruxolitinib. pERC noted that in the RESPONSE trial, the majority of patients continued to receive treatment at 80 weeks of follow-up even though only a fraction of patients met the study's primary endpoint after 32 weeks of follow-up. Therefore, pERC considered that it would be important from a quality-of-care perspective to assess patient response no later than 24 weeks after starting treatment, to ensure they are responding to ruxolitinib, and regularly thereafter to ensure patients are still responding to and benefiting from therapy. pERC also noted that a previous review`s recommendation of ruxolitinib in the treatment of myelofibrosis suggested monitoring at 24 weeks and this allowed for consistency across indications. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the submitter regarding monitoring no later than 24 versus 32 weeks after starting ruxolitinib. pERC reiterated that monitoring no later than 24 weeks after starting ruxolitinib was appropriate for the reasons previously stated.

Need: No curative treatment for patients with PV

Approximately 18.0% to 21.8% of patients have disease resistance to or intolerance of HU in the PV treated population. pERC noted that current treatments for PV are limited to prevention of complications and symptom control, and are not curative. The treatments currently used (phlebotomy, low-dose Aspirin, HU, busulfan, and anagrelide) are either marginally effective or are symptomatic treatments with limited duration of response.

PATIENT-BASED VALUES

Values of patients with polycythemia vera: Symptom reduction and improved quality of life

pERC deliberated upon patient advocacy group input concerning ruxolitinib for PV and discussed the values of patients with PV. The most frequently reported symptoms were cognitive impacts (difficulty concentrating, stress, anxiety), fatigue, itching, night sweats, and pain. Patients also reported negative impact on daily living. These symptoms translate into a substantial reduction in day-to-day functioning and QoL. pERC discussed this input and considered that the results of the RESPONSE trial support an improvement in these symptoms, increasing QoL and functioning of patients with PV.

Patient values on treatment: Limited effective treatment options

pERC discussed patient advocacy group input indicating that while currently available therapies may provide blood count control, they may not improve QoL and that there are a number of limitations with these treatments. For example, patients expressed concerns regarding treatments losing their effectiveness over time as well as significant side effects associated with HU and interferon. pERC considered that this input from the patient advocacy group further supported a need for new treatment options for PV. Patients indicated that they are willing to explore other treatment options that may have side effects with the treatment goals of delayed disease progression and a reduced or eliminated need for regular phlebotomies.

pERC noted that eight patients who provided input had direct experience with ruxolitinib. The patient advocacy group input indicated that these patients were all still on therapy, with some patients having two or more years of experience with ruxolitinib. Patients reported adverse events with ruxolitinib including nausea, diarrhea, and pain. However, none experienced serious effects or problems with the drug. Patients noted reductions in spleen size, less itching, less pain, and increased energy with treatment with ruxolitinib. pERC further considered that these reports from patients aligned with efficacy and QoL results that were observed in the RESPONSE trial and supported alignment of ruxolitinib with patient values. pERC also noted that detailed descriptions of patient experiences with ruxolitinib were very useful in determining whether there was alignment with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed an economic evaluation of the cost-utility of ruxolitinib compared with BAT in patients with PV, reflecting patients from the RESPONSE trial and the treatments that were used to treat patients with PV resistant to or intolerant of HU in this trial.

Basis of the economic model: Clinical and economic inputs

Costs considered in the model provided by the submitter included costs for drug acquisition, drug administration, disease management, thrombotic events, and end of life. The key clinical outcomes considered in the model provided by the submitter were WBC control, OS, and health state utilities. pERC noted that most of the appropriate factors were included in the model. However, pERC noted that the RESPONSE trial did not inform OS data in the submitted economic model; therefore additional published retrospective studies were used to inform this input.

Drug costs: High cost compared with other treatment options

Ruxolitinib costs $82.19 per 5 mg, 10 mg, 15 mg, or 20 mg tablet. At the recommended dose of 10mg twice daily (2 x 10 mg tablets), the average cost per day per 28-day course of ruxolitinib is $164.38, and the average cost per 28-day course is $4,602.73. pERC also discussed that ruxolitinib is priced per tablet and not per milligram, which is a potential barrier to implementation because actual use in clinical practice could increase costs significantly. Although this is not expected to be common dosing practice, depending on the combination of tablets used to provide a 20mg dose (e.g., 4 x 5 mg tablets) or the dose adjustments required to manage toxicity, the price of ruxolitinib may be as high as $328.77 per day and $9,205.48 per 28-day course.

Hydroxyurea costs $1.02 per 500 mg capsule. At the recommended dose of 500 mg twice daily, the average cost per day per 28-day course of hydroxyurea is $2.04 and the average cost per 28-day course is $57.14.

Peginterferon costs $399.40 per vial of 180 mcg/0.5mL. At the recommended dose of 90 mcg weekly for 2 weeks then escalated to 180 mcg once weekly, the average cost per day per 28-day course of peginterferon is $57.06 and the average cost per 28-day course is $1,597.60.

Anagrelide costs $3.35 per 0.5 mg capsule. At the recommended initial dose of 0.5 mg four times a day for at least one week and 1 mg to 4 mg daily, the average cost per day per 28-day course of anagrelide ranges from $8.37 to $26.79 and the average cost per 28-day course ranges from $234.44 to $750.20.

pERC noted that the price of ruxolitinib tablets is the same regardless of tablet strength. Therefore, dose reductions would not lead to a corresponding reduction in drug costs because the cost of the 5 mg, 10 mg, 15 mg and 20 mg tablets is the same. Dose escalations or dose reductions that result in multiple tablets may lead to substantial increases in drug costs. Some patients may require a dose as high as 25 mg twice daily, which would increase costs substantially. pERC noted other factors that could lead to increases in drug costs such as allowing patients to continue therapy who are no longer responding or had a poor initial response. pERC considered that it would be important for jurisdictions to consider measures to manage the monthly costs of ruxolitinib given it is a key driver of cost-effectiveness in the economic model.

Clinical effect estimates: Unknown impact on overall survival

pERC noted that there is a high level of uncertainty of the impact of ruxolitinib on long term survival outcomes given the majority of patients in the BAT group crossed over to ruxolitinib at 32 weeks. The Committee discussed that the submitted model was based on retrospective studies that linked WBC count or CHR from the RESPONSE trial to long-term survival outcomes. pERC noted that there is no strong evidence to indicate that either endpoint is an appropriate surrogate for OS. pERC noted and agreed with the CGP that based on the current level of evidence, the endpoint of CHR may be a more appropriate outcome in the cost-effectiveness analysis. Furthermore, pERC noted that the use of CHR or WBC control provided the most optimistic estimate of effect of ruxolitinib compared with standard therapy. Based on the current limited evidence, it is unclear how ruxolitinib would compare relative to standard therapies from a long-term efficacy or safety perspective.

Cost-effectiveness estimates: High cost of ruxolitinib a key driver

pERC deliberated upon the cost-effectiveness of ruxolitinib and noted that the EGP estimate of incremental cost-effectiveness ratios (ICERs) was higher than the manufacturer's estimate, primarily because the EGP used the endpoint of CHR over WBC control, which was considered more appropriate by the CGP. pERC concluded that at these more appropriate estimated incremental cost-utility ratios, ruxolitinib could not be considered cost-effective.

The ICERs were also quite sensitive to changes in the QoL utility values associated with treatment. The CGP did not support the large magnitude of difference in on-treatment utilities seen between the ruxolitinib and the best available therapy groups. Upon reconsideration of the pERC Initial recommendation, pERC discussed feedback received from the submitter regarding the pCODR Economic Guidance Panel (EGP) reanalysis which incorporated the same utility value for the ruxolitinib group and the best available therapy group. pERC acknowledged that the EGP revised their range of estimates to reflect the use of different utility values for the two treatment groups for the lower bound and the use of the same utility values for the two treatment arms for the upper bound. Furthermore, the high incremental cost associated with ruxolitinib was a key cost driver of the ICERs. pERC also discussed that there was uncertainty in the estimates of incremental cost due to the:

- flat per tablet pricing structure of ruxolitinib and possible dose adjustments that may require multiple strengths of tablets
- need for ongoing monitoring to ensure patients are responding to ruxolitinib
- potentially indefinite duration of treatment for patients
- dose tapering that is required upon discontinuation of ruxolitinib

Therefore, despite revisions in the EGP's range of estimates, pERC considered that there was considerable uncertainty in the cost-effectiveness estimates provided for ruxolitinib and therefore, the Committee concluded that ruxolitinib was not cost-effective compared to best available therapy.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Prevalent patient population

pERC discussed the feasibility of implementing a funding recommendation and noted that PV is an uncommon condition, therefore the burden of illness is likely small for the incident population. However, there may be a substantial population of prevalent cases requiring treatment with ruxolitinib. In addition, it was noted that patients may need to be treated in cancer treatment centres to allow for appropriate monitoring of toxicities and drug-to-drug interactions associated with ruxolitinib, which would increase workload in these clinics.

pERC also noted that to enhance feasibility and manage monthly drug costs, provinces may need to consider measures that include the following:

- monitoring for a response to treatment no later than 24 weeks after starting ruxolitinib
- ongoing monitoring for response as treatment duration may be indefinite
- tapering ruxolitinib dose when considering discontinuation because of the possible rebound effects
- considering the impact of dose adjustments on tablet burden since ruxolitinib is flat priced per tablet, not per milligram and actual use in clinical practice may significantly increase costs, depending on what combination of tablets is used
- stopping criteria based on disease progression.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from PAG regarding the definition of discontinuation criteria for treatment with ruxolitinib. pERC acknowledged that the treatment duration of ruxolitinib will be a substantial implementation issue and that there is currently no evidence to support or refute specific criteria for discontinuation. pERC noted and agreed with PAG that provincial tumour groups should work together to define an appropriate duration of treatment and assessment parameters at a national level to ensure consistency across the country.

DRUG AND CONDITION INFORMATION

Drug Information	• Tyrosine kinase inhibitor selective for Janus kinase (JAK) 1 and JAK2 • Available in 5 mg, 10 mg, 15 mg, and 20 mg tablets • Recommended starting dose of 10 mg orally twice daily for platelet count ≥ 100,000/mm^3 and 5 mg orally twice daily for platelet count of 50,000 to < 100,000/mm^3
Cancer Treated	• Polycythemia vera intolerant of or resistant to hydroxyurea (HU) • Primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis
Burden of Illness	• Incidence rate of approximately 2 cases per 100,000 per year • The median age of diagnosis is approximately 60 years with current survival of treated patients greater than 13 years
Current Standard Treatment	• Low-risk patients treated with intermittent phlebotomy, low-dose Aspirin and non-pharmacological interventions including lifestyle modifications • High-risk patients treated with hydroxyurea, interferon, busulfan, or anagrelide in addition to treatments for low-risk patients
Limitations of Current Therapy	• Available treatments are either marginally effective (cytoreductive therapy, Aspirin, no treatment, best supportive care) or provide transient relief of symptoms

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy-Thompson, Pharmacist
Valerie MacDonald, Patient Member-in-Training
Carole McMahon, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the initial recommendation except:

- Carole McMahon who did not vote due to her role as a patient member alternate
- Valerie MacDonald who did not vote due to her role as a patient member-in-training

All members participated in deliberations and voting on the final recommendation except:

- Paul Hoskins who was not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate
- Valerie MacDonald who did not vote due to her role as a patient member-in-training

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review ruxolitinib (Jakavi) for polycythemia vera, through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but none of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

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