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) **Submitter's Funding Request:** For the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.	
Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: June 19, 2012	**Submission Date:** June 25, 2012
Initial Recommendation: November 1, 2012	**Final Recommendation:** January 14, 2013

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding ruxolitinib (Jakavi) conditional on the cost-effectiveness of ruxolitinib being improved to an acceptable level. Ruxolitinib should be funded for patients with intermediate to high risk symptomatic Myleofibrosis as assessed using the Dynamic International Prognostic Scoring System (DIPSS) Plus or patients with symptomatic splenomegaly. Patients should have an ECOG performance status ≤3 and be either previously untreated or refractory to other treatment. The Committee made this recommendation because they were satisfied that there was a net clinical benefit for ruxolitinib based on improvements in quality of life and myelofibrosis symptoms, which were very important outcomes to patients, and because there are very limited treatment options for this group of patients with myelofibrosis. However, at the submitted price and based on the Economic Guidance Panel's best estimates, ruxolitinib could not be considered cost-effective compared with best available therapy, which was the control group used in the COMFORT II study.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness

Given pERC was satisfied that there was a net clinical benefit for ruxolitinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of ruxolitinib 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 improve cost-effectiveness to an acceptable level. These measures could address the following: monitoring for a response to treatment no later than 24 weeks after starting ruxolitinib; ongoing monitoring for response since treatment duration may be indefinite if patients continue to respond; the need for tapering ruxolitinib dose when considering discontinuation because of possible rebound effects; the impact of dose adjustments on tablet burden since ruxolitinib is priced per tablet, not per milligram and actual use in clinical practice may significantly increase costs.

SUMMARY OF pERC DELIBERATIONS

pERC noted that, other than allogenic stem cell transplant (ASCT) there are currently no curative treatments for myelofibrosis and other currently available therapies have limited efficacy on symptom control. pERC also noted that most patients with myelofibrosis are not candidates for ASCT, therefore, the Committee considered that there is a need for effective therapies to treat myelofibrosis. Two randomized controlled trials evaluating ruxolitinib compared with placebo (COMFORT I, Verstovsek 2012) and compared with best available therapy (COMFORT II, Harrison 2012) in patients with intermediate to high risk myelofibrosis, were included in the pCODR systematic review. pERC considered that these comparisons were appropriate given the available treatment options for myelofibrosis. pERC also noted that the patients evaluated in these trials included both those who were and were not previously treated for myelofibrosis and who were ineligible for ASCT.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

In deliberating on the results of COMFORT I and COMFORT II, overall survival analyses were discussed but pERC was uncertain that there was an overall survival advantage demonstrated for ruxolitinib. Neither of the trials were designed to detect a survival benefit and there was no difference between groups in overall survival at 24 weeks in COMFORT I or at 48 weeks in COMFORT II. pERC also noted that these survival analyses were likely confounded by the cross-over of patients from the control groups to the ruxolitinib groups. While an updated analysis from COMFORT I and a small observational study comparing ruxolitinib with historical controls (Verstovsek 2010) are both suggestive of a possible survival benefit with ruxolitinib over the long-term, pERC noted that the degree of uncertainty was such that the committee was unable to conclude that ruxolitinib improves overall survival in myelofibrosis.

pERC discussed other efficacy outcomes in the trials and noted that improvements favoring ruxolitinib were observed in the proportion of patients achieving a ≥35% reduction in spleen volume, the proportion of patients achieving a ≥50% reduction in total symptom scores and in mean change in quality of life scores. pERC noted that these outcomes were highly valued by patients due to their impact on daily functioning and that the results observed in the COMFORT I and COMFORT II trials aligned with patients' direct experiences, as reported in patient advocacy group input. The improvement in disease-related symptoms and quality of life were considered to be very important by the Committee. Therefore, pERC concluded that ruxolitinib was effective based on improvements in myelofibrosis symptoms and quality of life.

Based on feedback from the manufacturer and patient advocacy groups, pERC reconsidered the patient population for whom ruxolitinib funding should be recommended. pERC acknowledged that the patients who are likely to experience improved quality of life on ruxolitinib are those who are either symptomatic or have symptomatic splenomegaly. pERC noted that while patients were included in COMFORT I and COMFORT II based, largely, on their International Prognostic Scoring System (IPSS) score, this score does not include symptomatic splenomegaly. However, pERC considered that the majority of patients with symptomatic splenomegaly would likely fall within the intermediate to high risk IPSS categories. Furthermore, pERC also noted that in clinical practice, a new scoring system is in general use, the Dynamic International Prognostic Scoring System (DIPSS) Plus. A patient's risk category is assessed with this scoring system and the risk category can be expected to change over the course of their disease, unlike a patient's IPSS risk category. Therefore, pERC considered that the DIPSS Plus would be the most appropriate scoring system to assess eligibility for ruxolitinib funding. In addition, pERC considered that patients with symptomatic splenomegaly should also be eligible for ruxolitinib funding.

pERC also discussed the safety of ruxolitinib. It was noted that in COMFORT I and COMFORT II the most common adverse events observed with ruxolitinib were hematologic. pERC considered that these treatment-related toxicities are manageable adverse events commonly observed in oncology patients. pERC also noted that the adverse events described by patients who had direct experience with ruxolitinib, as reported in patient advocacy group input, aligned with those reported in the COMFORT I and COMFORT II studies. In addition, these patients considered the side effects of ruxolitinib to be tolerable. pERC also

noted that there are case reports of a rebound effect upon discontinuation of ruxolitinib (Tefferi 2012), although this was not observed in either the COMFORT I or COMFORT II studies. Therefore, pERC considered it important that when considering discontinuation of treatment, the ruxolitinib dose be appropriately tapered.

pERC reviewed patient advocacy group input and noted that the detailed descriptions of patients' experiences with ruxolitinib and the high quality of the input was very useful in determining if ruxolitinib aligned with patient values. pERC noted that patient input indicated that there are few treatments available for patients with myelofibrosis and that there is a need for effective therapies. pERC also noted that patients with direct experience with ruxolitinib had improvements in quality of life symptoms such as fatigue, and these improvements enabled them to return to normal activities. These benefits from treatment were highly valued by patients. These patients also noted that the side effects experienced with ruxolitinib were tolerable, when considering the benefits of symptom control and improved quality of life. Therefore, pERC considered that ruxolitinib aligned with patient values.

pERC also considered factors affecting the feasibility of implementing a recommendation for ruxolitinib. The Committee noted that myelofibrosis is an uncommon condition; therefore the burden of illness is likely small for the incident population. However, because there are currently only marginally effective treatments, there will be a population of patients in the community who will require treatment with ruxolitinib. The size of this patient population is unknown but it could be significant. pERC also noted that to enhance feasibility and manage monthly drug costs associated with ruxolitinib's use in actual practice, provinces may need to consider factors such as clear monitoring plans to evaluate patients for response, and the budget impact of a number of issues relating to dosing: 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.

pERC deliberated on the cost-effectiveness of ruxolitinib and agreed with the Economic and Clinical Guidance Panels that a time horizon of two to three years was most appropriate for use in the submitted economic model. 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. In discussing the cost-effectiveness estimates, pERC noted that despite the important improvements in symptoms and quality of life that were observed in COMFORT I and COMFORT II studies and described in patient advocacy group input, the incremental cost-effectiveness ratio was quite sensitive to small incremental changes in quality-adjusted life years. This was primarily due to the high incremental treatment costs associated with ruxolitinib. pERC also discussed that there was uncertainty in the estimates of incremental cost due to per tablet pricing of ruxolitinib and possible dose adjustments that may require multiple tablets; the need for ongoing monitoring to ensure patients are responding to ruxolitinib; the indefinite duration of treatment for patients who continue to respond to ruxolitinib; and 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.

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 two patient advocacy groups (The Chronic Myelogenous Leukemia (CML) Society of Canada and the Canadian Myeloproliferative Neoplasms (MPN) Network)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group.
- two patient advocacy groups (The CML Society of Canada and the Canadian MPN Network)
- the Submitter (Novartis Pharmaceuticals Canada Inc.)

The pERC Initial Recommendation was to recommend funding ruxolitinib conditional on the cost-effectiveness of ruxolitinib being improved to an acceptable level. Ruxolitinib should be funded in patients with intermediate-2 to high risk symptomatic myelofibrosis, ECOG performance status <3 who are previously untreated or refractory to other treatment. Feedback on the pERC Initial Recommendation indicated that the manufacturer and one patient advocacy group (The CML Society of Canada) agreed in part with the initial recommendation; pCODR's Provincial Advisory Group and one patient advocacy group (The Canadian MPN Network) agreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of ruxolitinib on patient outcomes compared with standard therapies, placebo, or best supportive care in the treatment of patients with splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis.

Studies included

The pCODR systematic review included two randomized controlled trials (RCTs) that evaluated ruxolitinib (15mg or 20 mg BID, dosed according to platelet counts), COMFORT I (Verstovsek 2012) and COMFORT II (Harrison 2012):

- COMFORT I was a double-blind RCT that compared ruxolitinib to placebo; cross-over upon progression could occur before the measurement of the primary endpoint at 24 weeks.
- COMFORT II was an open-label RCT that compared ruxolitinib to best available therapy; cross-over upon progression could occur either at 24 weeks or 48 weeks.

In addition, two non-randomized studies providing important contextual information were summarized in the pCODR Clinical Guidance Report: a survival analysis comparing ruxolitinib patients with historical controls (Verstovsek 2010) and a case series describing reports of rebound upon discontinuation of ruxolitinib (Tefferi 2011).

Patient populations: majority of patients with intermediate to high risk IPSS

COMFORT I included patients with myelofibrosis that was either refractory or intolerant to available therapies while COMFORT II included patients who were still eligible for some available treatments but unsuitable for ASCT. In both studies, patients had an Eastern Co-operative Oncology Group (ECOG) performance status score $\leq$3, palpable splenomegaly and were in the IPSS risk category of intermediate-2 or higher.

Based on feedback from the manufacturer and patient advocacy groups, pERC reconsidered the patient population for whom ruxolitinib funding should be recommended. pERC acknowledged that the patients who are likely to experience improved quality of life on ruxolitinib are those who are either symptomatic or have symptomatic splenomegaly. pERC noted that while patients were included in COMFORT I and COMFORT II based, largely, on their International Prognostic Scoring System (IPSS) score, this score does not include symptomatic splenomegaly. However, pERC considered that the majority of patients with symptomatic splenomegaly would likely fall within the intermediate to high risk IPSS categories. Furthermore, pERC also noted that in clinical practice, a new scoring system is in general use, the Dynamic International Prognostic Scoring System (DIPSS) Plus. A patient's risk category is assessed with this scoring system and the risk category can be expected to change over the course of their disease, unlike a patient's IPSS risk category. Therefore, pERC considered that the DIPSS Plus would be the most appropriate scoring system to assess eligibility for ruxolitinib funding. In addition, pERC considered that patients with symptomatic splenomegaly should also be eligible for ruxolitinib funding.

pERC considered this the appropriate patient population in which to study ruxolitinib but noted that although patients with higher ECOG performance status were eligible for these studies, the majority of patients (~86%) had an ECOG performance status $\leq$1. pERC also noted that approximately two-thirds of patients in both studies had prior experience with hydroxyurea, a common treatment for myelofibrosis.

Key efficacy results: improvements in symptom burden and spleen volume

The primary endpoint in both studies was the proportion of patients achieving a $\geq$35% reduction in spleen volume as measured at 24 weeks in COMFORT I and as measured at 48 weeks in COMFORT II.

Other key efficacy outcomes deliberated upon by pERC were the proportion of patients achieving a ≥50% reduction in total symptom scores, based on the modified Myelofibrosis Symptom Assessment Form, and overall survival.

A higher proportion of patients in the ruxolitinib group achieved ≥35% reduction in spleen volume compared with the placebo group in COMFORT I at 24 weeks (41.9% versus 0.7%, respectively) and compared with the best available therapy group in COMFORT II at 24 weeks (31.9% versus 0%, respectively) and at 48 weeks (28.1% versus 0, respectively). In COMFORT I, a higher proportion of patients in the ruxolitinib group compared with the placebo group achieved ≥50% reduction in total symptom score at week 24 (45.9% versus 5.3%, respectively, P<0.001). 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.

There was no difference between groups in overall survival at 24 weeks in COMFORT I or at 48 weeks in COMFORT II. However, pERC noted that these analyses are likely confounded by cross-over of patients from the control group to the ruxolitinib group. In addition, an updated survival analysis (with median 51 weeks of follow-up) from COMFORT I was significant (hazard ratio 0.50, 95% confidence interval: 0.25 to 0.98, P=0.04). pERC also noted that a non-randomized study comparing ruxolitinib patients with historical controls (Verstovsek 2010) suggested a survival benefit. When taking these different analyses into account, pERC considered it possible that ruxolitinib could have a survival benefit but that the evidence was not strong enough as yet to determine this with certainty.

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

Quality of life was evaluated in both COMFORT I and COMFORT II using the European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire (EORTC QLQ-C30). This consists of five subscales on function (i.e., physical, role, emotional, cognitive, social), a global health status and quality of life composite score, and individual symptom subscales (e.g., fatigue, pain, nausea).

In COMFORT I at 24 weeks, mean changes from baseline to week 24 were significantly improved in ruxolitinib-treated patients for all subscales except cognitive functioning, while a worsening in each subscale was reported for placebo-treated patients. Limited quality of life data were reported in COMFORT II. However, it showed a greater improvement in the global health status and quality of life composite score in the ruxolitinib group compared with the best available therapy group. pERC considered that these improvements in quality of life were consistent with reductions in spleen volume and symptoms that were observed in the COMFORT I and COMFORT II studies. In addition, pERC noted that improvements in quality of life 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 quality of life improved following ruxolitinib treatment due to a decrease in fatigue and reductions in their spleen size which permitted better functioning and allowed them to resume normal activities.

Safety: hematologic adverse events manageable, possible rebound upon discontinuation

pERC discussed the adverse events observed in COMFORT I and COMFORT II. The proportion of patients with grade 3 or grade 4 adverse events was similar between ruxolitinib and placebo in COMFORT I, but was higher in ruxolitinib-treated patients compared with best available therapy in COMFORT II (42% versus 25%, respectively). However, pERC noted that the majority of adverse events were hematologic such as anemia, thrombocytopenia or neutropenia and these types of adverse events are routinely managed by haematologists and oncologists when caring for patients with cancer. pERC also considered patients' direct experiences of side effects with ruxolitinib based on patient advocacy group input. pERC noted that these descriptions of side effects aligned with the adverse events reported in COMFORT I and COMFORT II but that patients considered the side effects of ruxolitinib to be tolerable given its potential benefits.

There were no reports of a rebound effect upon discontinuation of ruxolitinib in COMFORT I or COMFORT II. However, pERC discussed a case series (Tefferi 2011) reporting on five patients who experienced rebound following discontinuation of ruxolitinib. pERC considered this a potentially serious adverse effect of ruxolitinib and noted that if discontinuation of ruxolitinib is being considered, the dose should be tapered as recommended in the product monograph.

Treatment duration: Indefinite treatment length requires monitoring for response
pERC discussed that the duration of treatment with ruxolitinib is possibly indefinite if patients continue to respond to ruxolitinib. Therefore, pERC considered that it would be important to assess patient response no later than 24 weeks after starting treatment, as in the COMFORT I trial, to ensure they are responding to ruxolitinib, and regularly thereafter to ensure patients are still responding and benefitting from therapy.

Need: no curative treatments for patients who are not candidates for transplant
pERC noted that currently the only curative therapy for myelofibrosis is ASCT, which is not available to most individuals because of age, co-morbidity or availability of donor. The treatments currently used are either marginally effective (splenectomy, cytoreductive therapy, supportive care with transfusions) or are symptomatic treatments with limited duration of response (hydroxyurea). Therefore, pERC considered that there is clear clinical need for effective treatments for myelofibrosis. Upon reconsideration of the pERC Initial Recommendation and based on feedback from patient advocacy groups the Committee discussed the definition of best available therapy. pERC noted that in the COMFORT II study and the submitted economic analysis, the best available therapies used in the control group were those treatments that were being used to treat myelofibrosis at the time, even though their effectiveness may have been minimal.

PATIENT-BASED VALUES

Values of patients with myelofibrosis: symptoms decrease quality of life and functioning
pERC considered patient advocacy group input highlighting that patients with myelofibrosis experience a number of symptoms that significantly interfere with daily activities such as night sweats, fatigue, shortness of breath, pain, enlarged spleen resulting in abdominal swelling, loss of appetite, weight loss, rash/itching and fever. These symptoms translate into a substantial reduction in day-to-day functioning and quality of life. pERC discussed this input and considered that the results of the COMFORT I and COMFORT II studies support an improvement in these symptoms, increasing the quality of life and functioning of patients with myelofibrosis.

Patient values on treatment: current treatments do not improve quality of life
pERC discussed patient advocacy group input indicating that while currently available therapies may prolong life, they may not improve quality of life and that there are a number of limitations with these treatments. For example, patients expressed concerns about secondary infections, risk of death, and other complications that may arise from invasive interventions such as splenectomy or transplants. In addition, patients cite that nausea, fatigue, diarrhea, abnormal liver function tests, and abnormal blood cell counts are side effects of currently available treatment options that are the most concerning. pERC considered that this input from patient advocacy groups further supported a need for new treatment options for myelofibrosis. Despite these concerns, patients indicated that they are willing to explore other potential treatment options that may have side effects provided that they understand the potential benefits for their quality of life.

Patients with direct experience with ruxolitinib indicated that they experienced a significant improvement in quality of life that allowed them to continue to work and spend time with their families. Moreover, patients indicated that ruxolitinib was more effective than any other therapy they had previously undergone and that overall, it was very well tolerated. pERC further considered that these reports from patients aligned with efficacy results that were observed in the COMFORT I and COMFORT II studies and supported alignment of ruxolitinib with patient values. pERC also noted that having high quality patient input, which was based on objective assessments through a structured survey and which provided detailed descriptions of actual patient experiences with ruxolitinib, was very useful in determining whether there was alignment with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost effectiveness model

The pCODR Economic Guidance Panel assessed an economic evaluation of the cost-utility of ruxolitinib compared to best available therapy in patients with myelofibrosis, reflecting patients from the COMFORT II study and the treatments that were used to treat myelofibrosis in this study.

Basis of the economic model: clinical and economic inputs

Costs included drug costs and healthcare costs associated with routine follow-up of patients receiving active treatment, costs of managing adverse events, leukemic transformation, and palliative care. The key cost driver was the cost of ruxolitinib.

Key clinical effects included quality of life data from COMFORT II (Harrison 2012) and survival data from a non-randomized study comparing ruxolitinib patients with historical controls (Verstovsek 2010). An implicit model assumption around a survival benefit and the extrapolation of long-term clinical benefit based on short term data had a pronounced effect on clinical effect estimates.

Drug costs: potential increased ruxolitinib costs due to tablet pricing and non-responders

At the list price, ruxolitinib costs $82.19 per 5 mg, 15 mg, or 20 mg tablets. At the recommended dose of 15 mg twice daily, the average cost per day in a 28-day course of ruxolitinib is $164.38 and the average cost per 28-day course is $4,602.64.

pERC noted that the price of ruxolitinib tablets is the same regardless of dose. Therefore, dose reductions would not lead to a corresponding reduction in drug costs because the cost of the 5 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 25mg 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 cost of ruxolitinib given it is a key driver of cost-effectiveness in the economic model.

Cost-effectiveness estimates: shorter time horizon increases incremental cost utility ratio

pERC deliberated upon the cost-effectiveness of ruxolitinib. It was noted that the Economic Guidance Panel's best estimate of the incremental cost-utility ratio is between $276,191 and $383,686 per QALY when ruxolitinib is compared to best available therapy pERC noted that this estimate was higher than the manufacturer's estimate, primarily because the Economic Guidance Panel used a shorter time horizon of two to three years, which was considered more appropriate by the Clinical Guidance Panel. pERC concluded that at these estimated incremental cost-utility ratios, ruxolitinib could not be considered cost-effective.

Upon reconsideration of the pERC Initial Recommendation and based on feedback from the manufacturer, pERC discussed the time horizon that was used in the analysis. pERC noted a key economic modeling consideration is whether the time horizon is sufficient to capture all of the costs and effects associated with treatment and that a lifetime time horizon is not always required to do this. The pCODR Clinical Guidance Panel had considered that a time horizon of approximately 150 to 200 weeks would be sufficient to capture these costs and effects. pERC also noted that the Economic Guidance Panel's best estimates were limited by the inherent structure of the submitted model, which did not permit adjustments to the time horizon parameter beyond what was originally provided (24 weeks, 48 weeks, 96 weeks, 144 weeks, and lifetime). Therefore, pERC considered that the pCODR Economic Guidance Panel's approach of applying a three year time horizon was reasonable in these circumstances.

pERC also noted that the pCODR Economic Guidance Panel identified a calculation error in the submitted economic analysis, which led to substantially higher cost-effectiveness estimates than were originally estimated by the Panel.

In discussing the incremental cost-effectiveness estimates, pERC noted that despite the important improvements in symptoms and quality of life that were observed in the COMFORT I and COMFORT II

studies and that were further described in patient advocacy group input, the incremental cost-effectiveness ratio was sensitive to small incremental changes in quality-adjusted life years. This was due to the very high incremental treatment costs associated with ruxolitinib. pERC also discussed that there was uncertainty in the estimates of incremental cost due to per tablet pricing of ruxolitinib and possible dose adjustments that may require multiple tablets; the need for ongoing monitoring to ensure patients are responding to ruxolitinib; the indefinite duration of treatment for patients who continue to respond to ruxolitinib; and 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.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: impact of prevalent population and managing of monthly ruxolitinib costs

pERC discussed the feasibility of implementing a funding recommendation for ruxolitinib and noted that myelofibrosis is an uncommon condition, therefore the burden of illness is likely small for the incident population. However, because there are currently only marginally effective treatments, there may be a significant population of prevalent cases requiring treatment with ruxolitinib. In addition, it was noted that 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.

pERC also noted that to enhance feasibility and manage monthly drug costs, provinces may need to consider factors such as monitoring patients for response, the impact of dose adjustments and dose tapering on budget impact and the impact of ruxolitinib being priced per tablet rather than per milligram.

Upon reconsideration of the pERC Initial Recommendation, pERC noted that the PAG agreed with the pERC Initial Recommendation and considered it feasible to implement, therefore, pERC did not deliberate further on the PAG feedback.

DRUG AND CONDITION INFORMATION

Drug Information	• Tyrosine kinase inhibitor selective for Janus kinase (JAK) 1 and JAK2 • 5 mg, 15 mg and 20 mg tablets reviewed by pCODR • recommended dosage of 15 mg or 20 mg orally BID, depending on platelet count
Cancer Treated	• Myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.
Burden of Illness	• Incidence rate of 0.2 - 1.5 cases per 100 000 per year. Majority of patients experience poor or very poor quality of life.
Current Standard Treatment	• Allogeneic stem cell transplant curative but not all patients are candidates due to age, co-morbidities or donor availability • For the vast majority of patients, therapy aims to reduce symptoms related to splenomegaly and cytokine release.
Limitations of Current Therapy	• Available treatments are either marginally effective (splenectomy, cytoreductive therapy, supportive care with transfusions), not applicable to most patients (ASCT) or do little to improve quality of life

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. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

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

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

- Dr. Allan Grill and Dr. Chaim Bell who were absent from the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

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 of ruxolitinib (Jakavi) for myelofibrosis, through their declarations, five 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

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).