Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**ruxolitinib**
Brand Name	Jakavi®
Dosage Form(s)	5 mg and 10 mg tablets
Manufacturer	Novartis Pharmaceuticals Canada Inc.
Submission Type	**New Submission**
Use Reviewed	For the treatment of **acute** Graft versus Host Disease (aGvHD) in patients aged 12 years and older.
Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews (CRR)	Yes, the CRR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CRR website for more details: Ruxolitinib (Jakavi) (cadth.ca)
Drug Benefit Council (DBC)	The DBC met on October 3, 2022. The DBC considered various inputs including: the final reviews completed by the CADTH CRR on September 15, 2022, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC received no Patient Input Questionnaire responses from patients, caregivers, or patient groups. Patient input provided to the CDR was considered, as well as a Budget Impact Assessment.

Drug Coverage Decision	**Limited Coverage Benefit** **Access the ruxolitinib criteria from www.gov.bc.ca/pharmacarespecialauthority**
Date	**November 23, 2023**
Reason(s)	**Drug coverage decision is consistent with the CDEC and DBC recommendations.** • Evidence from a clinical trial demonstrated that people with steroid refractory or dependent aGvHD treated with ruxolitinib experienced responses related to the resolution of signs and symptoms of GvHD. • Ruxolitinib met patient needs of providing an oral drug option with manageable side effects that can be administered as an outpatient treatment. • Based on economic considerations and the submitted product price, ruxolitinib was not cost effective for this indication. • The Ministry participated in the pan-Canadian Pharmaceutical Alliance negotiations with the manufacturer which were able to address the concerns identified by the CDEC with respect to the cost-effectiveness and value for money**.**
Other Information	In addition to the aGvHD indication, ruxolitinib was reviewed for chronic graft-versus-host disease (cGvHD) and as of November 23, 2023, ruxolitinib (Jakavi®) is covered as Limited Coverage benefit for both indications.

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews(CRR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Appendix

CONFIDENTIAL

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Ruxolitinib (Jakavi®)
Novartis Pharmaceuticals Canada Inc.

Description:

Drug review of **ruxolitinib (Jakavi®)** for the following Health Canada approved indication:

> For the treatment of Acute Graft versus Host Disease (aGVHD) in patients who have inadequate response to corticosteroids or other systemic therapies.

In their review, the DBC considered the following: the final reviews completed by the Canadian Agency for Drugs and Technologies in Health (CADTH) on September 15, 2022, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC received no Patient Input Questionnaire responses from patients, caregivers, or patient groups. Patient input provided to the CDR was considered, as well as a Budget Impact Assessment.

Dosage Forms:

Jakavi® is available as ruxolitinib 5 mg, 10 mg, 15 mg, and 20 mg tablets.

Recommendations:

1. The Drug Benefit Council (DBC) recommends not to list ruxolitinib (Jakavi®) at the submitted price for aGVHD.

Of Note:

- If the Ministry is able to negotiate a significant price reduction, the reimbursement criteria and conditions recommended by CDEC are an appropriate basis for coverage.

Reasons for the Recommendation:

1. **Summary**

- Evidence from one single-arm phase II pivotal trial demonstrated that ruxolitinib achieved the predetermined threshold for a positive objective response rate (ORR) at Day 28.
- Evidence from one phase III, open-label, multi-centre randomized controlled trial (RCT) provided supportive evidence and demonstrated that compared with best available therapy (BAT) ruxolitinib was associated with statistically significant improvements in ORR at Day 28, and durable ORR at Day 56.
- There was uncertainty regarding the magnitude of clinical benefit directly attributable to ruxolitinib due to limitations associated with the design of both trials.
- CADTH was unable to determine a cost-effectiveness estimate for the treatment of patients aged 12 years and older with steroid refractory (SR) or dependent aGvHD. A price reduction from the manufacturer's submitted price would increase the probability of ruxolitinib being considered cost-effective.

2. **Clinical Efficacy**

- The DBC considered the CADTH systematic review, which included an open-label, single-arm, multi-centre phase II trial that evaluated the efficacy and safety of ruxolitinib in combination with corticosteroids in patients with Grades II to IV SR-aGvHD (REACH 1); and a multi-centre, randomized, phase III, open-label trial comparing the efficacy and safety of oral ruxolitinib with the Investigator's choice of BAT in patients 12 years of age or older who had SR-aGvHD after allogeneic stem cell transplantation (alloSCT) (REACH 2).
- Because of uncertainties around REACH 2 identified by the FDA upon the review of raw data from the trial, Health Canada reviewed efficacy and safety data from REACH 1 as the pivotal study and the safety data from REACH 2 as supportive evidence for the aGvHD indication. The CADTH review was based on data from REACH 1 final data cut-off date; and REACH 2 data from the primary analysis, updated secondary analysis, and the final analysis, which was conducted once all patients had completed the study.
- The primary outcome of REACH 1 was objective response rate (ORR) at Day 28 and the key secondary outcome was duration of response (DOR) at Month 6. Additional secondary outcomes were overall survival (OS), failure free survival (FFS), ORR at Day 14, DOR at Month 3, non-relapse mortality (NRM), incidence of malignancy relapse/progression, relapse rate, relapse related mortality rate, and safety.
- REACH 1 demonstrated that ruxolitinib achieved the predetermined threshold for a positive objective response rate (ORR) at Day 28. The proportion of patients who achieved ORR at Day 28 was 56.3%. REACH 1 also showed that ruxolitinib met the trial's pre-specified efficacy outcome threshold for ORR in patients who had corticosteroid refractory or dependent aGvHD.

- No definitive conclusion could be reached regarding the effects of ruxolitinib on health-related quality of life (HRQoL) as such data were not collected in REACH 1.
- REACH 1 had an open-label design whereby the Investigator and the participants were aware of their treatment status, which increased the risk of detection and performance bias. This had the potential to bias results in favour of ruxolitinib if the assessor (Investigator or patient) believed the study drug is likely to provide a benefit.
- While REACH 1 achieved the predetermined threshold for a positive outcome in patients who received ruxolitinib, there was uncertainty regarding the magnitude of clinical benefit directly attributable to ruxolitinib due to the limitations associated with the study design, including the single-arm, open label trial design with no formal statical significance testing, and relatively small sample size.
- REACH 2 provided supportive evidence and demonstrated that compared with BAT ruxolitinib was associated with statistically significant improvements in ORR at Day 28, and durable ORR at Day 56.
- The open label design of REACH 2 and reliance on local Investigator's assessment of trial outcomes, may have introduced a bias that is difficult to quantify.
- For detailed information on the systematic review of ruxolitinib for aGVHD please see the CDEC Final Recommendation at: https://www.cadth.ca/ruxolitinib.

3. Safety

- The most commonly reported treatment-emergent adverse events (TEAEs) were similar between the REACH 1 and REACH 2 trials and included anemia (64.8%), thrombocytopenia (62.0 %), hypokalemia (49.3 %), neutropenia (47.9 %), and oedema peripheral (46.5 %).
- While in REACH 2 ruxolitinib appeared to have more adverse events than BAT, the clinical experts consulted by CADTH noted that most TEAEs associated with ruxolitinib could be managed with dose modifications and best supportive care.
- For detailed information on the safety and tolerability of ruxolitinib for aGVHD, please see the CDEC Final Recommendations at the links above.

4. Economic Considerations

- The cost-effectiveness of ruxolitinib is highly uncertain due to uncertainty in the sponsor's post hoc analysis of REACH 2 trial data, which was used to populate the majority of model parameters, along with concerns regarding the model structure not adequately capturing the complexity of steroid-refractory aGVHD.
- As such, a base-case cost-effectiveness estimate was unable to be determined for the treatment of patients aged 12 years and older with steroid-refractory or steroid-dependent aGvHD. Price reductions are likely required to increase the probability of ruxolitinib being cost-effective.

5. Of Note

- There is currently no standard of care for patients who have steroid-refractory or steroid-dependent aGvHD. Patient input provided to CADTH emphasized a need for