CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

RUXOLITINIB (Jakavi)

Novartis Pharmaceutical Canada Inc.

Indication: For the treatment of chronic graft-versus-host disease in patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies.

June 30, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0706-000
Brand name (generic)	Jakavi (Ruxolitinib)
Indication(s)	For the treatment of chronic graft-versus-host disease in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies
Organization	Ontario Health (Cancer Care Ontario) Complex Malignant Hematology
Contact information[a]	Name: Dr. Tom Kouroukis

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

On page 4, Section for Renewal, it says that Treatment with ruxolitinib should be renewed for patients who have achieved an overall response (i.e. CR or PR), according to NIH criteria -> we suggest this should be rephrased. Patients having a clinical benefit with ruxolitinib (i.e. stable disease but with significant reduction of steroid) should be allowed for renewal of ruxolitinib.

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
OH-CCO provided secretariat support in completing this feedback.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Tom Kouroukis		

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CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0706
Name of the drug and Indication(s)	Jakavi (ruxolitinib) for the treatment of chronic graft-versus-host disease in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. Suggest that initiation (point 2) reflects previous section: “corticosteroid refractory and other systemic therapies”. For renewal (point 3), please clarify whether no response translates to progression of the disease (or stable). Clarify overlap of renewal and discontinuation criteria. Alternatively, consider adding to discontinuation criteria. For prescribing (point 5.2), toxicity not normally included in prescribing conditions.

c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0706-000 Stakeholder Feedback on Draft Recommendation
Brand name (generic)	Jakavi (ruxolitinib)
Indication(s)	Graft versus host disease
Organization	Lymphoma and Leukemia Society of Canada (LLSC), CLL Canada
Contact information[a]	Name: Sabrina Hanna (LLSC) [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

We agree with the draft recommendation to reimburse ruxolitinib - given that patients cited a need for a treatment that helped relieve symptoms associated with GvHD and with less toxicity than other currently available treatments. In regard to the rationale that only clinicians who are have experience with GvHD and the toxicity profile of GvHD, we would just like to note that patients will see a host of specialists for symptoms related to GvHD, most of whom will not be familiar with GvHD or ruxolitinib. Patients can be misdiagnosed and given treatments that worsen symptoms related to GvHD before being seen by a clinician who specializes in GvHD and would be familiar with ruxolotinib. This is particularly an issue for patients living far from their treatment center, and not just in rural areas. For example, we know of a patient with GVHD who lives in St-John's Newfoundland who underwent his stem cell transplant in Halifax and must travel there each time he has to see his specialist.

For patients who live far from a major cancer center, it is very costly in time and money to see a specialist to be prescribed ruxolitinib. Indeed, the respondents to our survey considered it to be very important to be able to access treatment locally and in an outpatient setting, avoiding the need for travel and hospital stays. The committee should recommend that provinces enable doctors in areas far from major cancer centres to prescribe ruxolitinib. It should also recommend that, as a matter of course, all patients who could suffer from GVHD be informed of this treatment option and how to obtain it.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

While the report provides a good summary of the input provided, it is also important to reiterate that patients are frustrated they have to undergo many treatments, many of which have severe side effects and require multiple visits to the hospital centre before being properly diagnosed and receiving ruxolitinib when reviewing the recommendations and conditions.

Clarity of the draft recommendation

3. **Are the reasons for the recommendation clearly stated?**	Yes	
	No	X

The reasons for Reimbursement condition 4, Discontinuation, are not clear. Is the "*lack of evidence that patients who exhibit the clinical presentations outlined in this condition would benefit from further treatment with ruxolitinib"* due to the fact that studies demonstrate the lack of benefit or is due to the absence of data which demonstrates a benefit? A lack of evidence is not necessarily evidence of lack.

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4. **Have the implementation issues been clearly articulated and adequately addressed in the recommendation?**	Yes	X
	No	☐

We reiterate what we wrote in answer to Question 1: issues faced by patients living far from cancer centres are not adequately addressed and doctor's who are not specialist with GvHD will require appropriate education on ruxolitinib in order to prescribe it for patients living where a GvHD specialist is not accessible. We know from lived experience that most patients will be misdiagnosed multiple times before receiving the appropriate diagnosis and clinician education will be critical. And as a matter of course, all patients who could suffer from GVHD be informed of this treatment option and how to obtain it.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

While we do not have the expertise to comment on economic evaluations, we would like to note that cost-effectiveness should also take into consideration in this case that patients had less treatment related toxicities that required in hospital care, they had a reduction of symptoms related to GvHD, an improvement in QoL, and also did not require them to receive treatment in hospital - all of which significantly impact the burden on the healthcare system and healthcare budgets.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Sabrina Hanna*
Position	*Advocacy Lead*
Date	*29.06.2022*
X	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	X
The organizations listed above contributed to the feedback.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	X
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☐	X	☐	☐
Add company name	☐	☐	☐	☐

Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0706
Brand name (generic)	ruxolitinib
Indication(s)	For the treatment of chronic graft-versus-host disease in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies
Organization	Novartis Pharmaceutical
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

- Novartis agrees with the CADTH Canadian Drug Expert Committee (CDEC) to recommend that "ruxolitinib be reimbursed for the treatment of chronic graft versus-host disease (cGvHD) in in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies." (Recommendation, page 3)
- Novartis also agrees with the input from clinical experts and patients on the unmet medical need: "Based on the input from clinical experts and patients, CDEC acknowledged this is a rare patient population with a significant unmet medical need for additional effective and safe treatment options in the cGvHD setting given the severe nature of this disease with substantial morbidity." (Rational for recommendation, page 3)
- Novartis agrees also on the efficacy of ruxolitinib: "CDEC acknowledged input from the clinical experts consulted by CADTH noting that the difference between patients who either have an inadequate response to corticosteroids alone or to multiple therapies would be unlikely to impact the treatment effect of ruxolitinib." (Discussion points, page 6)
- Novartis agrees with CADTH on the safety profile: "no unexpected safety concerns were observed with ruxolitinib, and patients could be adequately managed in clinical practice." (Discussion points, page 6)
- Novartis agrees with CDEC on the similar treatment effect and safety profile among adults and adolescents aged 12 to 18 years. (Discussion points, page 6)

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?
Although Novartis agrees with the CADTH CDEC on the clinical part, several comments made by Novartis on the reports regarding the economic evaluation were not taken into account by the committee (duration of response, dosing of BAT more particularly).

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.
Novartis doesn't agree on the reimbursement condition regarding the renewal criteria (Table 1, page 4):
"Treatment with ruxolitinib should be renewed for patients who have achieved an overall response (i.e., CR or PR), according to NIH criteria, after 24 weeks of therapy (approximately 6 months)"

- ⇨ Treatment with ruxolitinib should be renewed for patients who have achieved an overall response: CR, PR and **Stable disease**. With over 350 patients in the MAP, more than 50 patients that are classified "stable disease" and at resupply intervals of 3 months continue to receive ruxolitinib because of clinical benefit as deemed by prescribing physician due to a 50% reduction of steroids or complete discontinuation of steroids. Long term use of steroids are associated with serious complications and higher mortality risk. Clinical experience indicates that clinically important qualitative improvement often occurs before improvement in the objective measures. For example, "stable" disease might be considered a meaningful response when the prior trajectory was clear progression, as indicated, for example, by serial pulmonary function tests or rapidly progressive sclerosis or reduction/cessation of concomitant steroid use. (Lee SJ, et al. Biol Blood Marrow Transplant. 2015; 21:984-99). While renewing treatment in patients with Stable disease also provides clinical benefit, physicians use clinical judgement to taper or discontinue ruxolitinib where the situation warrants to ensure that a flare-up of GVHD symptoms does not occur leading to poor outcomes.

[a] CADTH may contact this person if comments require clarification.