CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

ibrutinib (Imbruvica)

(Janssen Inc.)

Indication: Imbruvica, as a single agent or in combination with rituximab, for previously treated, relapsed/refractory (RR) Waldenström's Macroglobulinemia (WM).

December 14, 2023

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting stakeholder group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0328
Brand name (generic)	Imbruvica (ibrutinib)
Indication(s)	Imbruvica, as a single agent or in combination with rituximab, for previously treated, relapsed/refractory (RR) Waldenström's Macroglobulinemia (WM).
Organization	Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
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	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

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?		

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. There needs to be more clarity in using rituximab in combination with ibrutinib.		
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.		

[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		
2. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
If yes, please detail the help and who provided it. OH-CCO provided a secretariat function to the group.		
3. 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		
4. 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 • Dr. Pierre Villeneuve		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
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	PC0328
Name of the drug and Indication(s)	Ibrutinib, with or without rituximab, for the treatment of adult patients with previously treated refractory or relapsed Waldenstrom's macroglobulinemia
Organization Providing Feedback	PAG

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.

Under Reimbursement Condition (1): PAG requested clarification that the recommendation applies to ibrutinib monotherapy, but not ibrutinib along with rituximab.
Under Reimbursement Condition (1.3): PAG noted that Table 2 specified IWWM-7, but the reimbursement condition only mentioned IWWM.
Under Reimbursement Condition (2.1): PAG requested clarification whether re-treatment is allowed if a patient was treated with a prior BTKi, discontinued treatment, then had disease progression while off treatment.

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. In Table 2, under Considerations for initiation of therapy (p. 8-11), PAG requested clarification of pERC's assessment of the clinical expert's responses and of pERC's final ruling. In Table 2, under Considerations for initiation of therapy, regarding ibrutinib monotherapy or in combination with rituximab (first row, p. 9), PAG requested a statement reiterating that pERC does not recommend combination treatment.

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

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0328-000
Brand name (generic)	Imbruvica (Ibrutinib)
Indication(s)	Imbruvica, as a single agent or in combination with rituximab, for previously treated, relapsed/refractory (RR) Waldenström's Macroglobulinemia (WM).
Organization	Lymphoma Canada
Contact information[a]	Name: [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.

We agree with the committee's recommendation that Ibrutinib be reimbursed for the treatment of relapsed or refractory Waldenström Macroglobulinemia. WM lymphoma patients have expressed the need for more effective treatments that extend survival, have fewer side effects, and improve quality of life. Additionally, it is important to patients that they have more choice of treatments that will be better tolerated and best suited to their personal clinical history. As noted by one of our surveyed patients, "Having a choice between chemo and newer treatment is important as it provides options for relapse, allergies, and other health issues a patient might have". Overall, the patients we surveyed rated their experience with this treatment as good, and would recommend it to other patients with R/R WM. In this regard Ibrutinib has addressed patient preferences with respect to choice, fewer side effects as well as longer progression free survival.

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?

Yes, the committee has demonstrated that it has recognized the importance of the preferences of the surveyed patient population, namely that patients would like more treatment options available to them. Access to more options in the relapsed/refractory setting that allow them to live longer, with less symptoms and an improved quality of life were important to patients surveyed.

Quotes from patients:

- "I am very happy taking Ibrutinib for my treatment of WM"
- "Ibrutinib makes me more energetic and cognitively sharp"
- "Ibrutinib saved my life. CVP-R had failed after third series, and then I suffered an attack of CIDP that completely paralyzed me. Prednisone and Ibrutinib brought me back."

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. Yes, reasons for the recommendation have been clearly stated.		
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. Yes, Table 1 “Reimbursement Conditions and Reasons” clearly states this information. However, for reimbursement condition 4, it is important to consider that in the event of side effects, clinical experts have noted that a dose-reduction could be considered, as lower doses can maintain efficacy with a more favourable side effect profile. Failure of efficacy is typically noted through new progressive cytopenia’s (anemia most commonly) and increases in IgM monoclonal protein.		

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Gurjot Basra*
Position	*Manager of Patient Programs, Research, and Advocacy*
Date	*24-12-2023*
☒	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	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	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**
Janssen	☐	☐	☐	☒
AstraZeneca	☐	☐	☐	☒
BeiGene	☐	☐	☐	☒

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0328-000-000
Brand name (generic)	Imbruvica (ibrutinib)
Indication(s)	Waldenströms Macroglobulinemia
Organization	The Leukemia & Lymphoma Society of Canada (LLSC)
Contact information[a]	Name: Colleen McMillan, Advocacy Lead, LLSC [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
We agree that ibrutinib may meet patients' need for survival without progression and improvement in hemoglobin levels which are linked to improvement in health-related quality of life. We thank the committee for their support and for considering the significant benefit to patient survival and quality of life that this treatment may provide.		

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	☐
LLSC did not submit stakeholder input in earlier stages of this review, however, our community supports the input submitted by the clinicians, The Waldenström's Macroglobulinemia Foundation of Canada and Lymphoma Canada in their submissions.		

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.		

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

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A. Patient Group Information	
Name	*Colleen McMillan*
Position	*Advocacy Lead*
Date	*07-12-2023*
☒	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	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	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**
Janssen Inc.	☐	☐	☐	☒
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0328 Imbruvica
Brand name (generic)	IMBRUVICA® (Ibrutinib)
Indication(s)	IMBRUVICA®, with or without rituximab, for the treatment of adult patients with previously treated refractory or relapsed Waldenström's Macroglobulinemia
Organization	Janssen Inc.
Contact information[a]	[redacted]

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

Janssen agrees with the committee's assessment of the clinical evidence from the pivotal trials iNNOVATE and PCYC-1118E, and is satisfied with the recognition of the added clinical value of Ibrutinib, as a single agent or in combination with rituximab, as a well tolerated targeted therapy.

However, the statement "*available evidence suggests ibrutinib has a less favourable safety profile*" is misleading as Zanubrutinib will have a less favorable safety profile for patients at high risk of neutropenia. Furthermore, pERC indicated in their deliberations "*lower doses (of ibrutinib) can maintain efficacy with a more favourable side effect profile*", whereas Zanubrutinib does not have an approved dose modification protocol to manage adverse events. Janssen kindly requests the first statement to be modified to provide more context regarding the safety profile of Ibrutinib and indicate that Zanubrutinib's tolerability profile is different than Ibrutinib's.

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?

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.		

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