CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

Ibrutinib (Imbruvica)

Janssen Inc.

Indication: Imbruvica with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion.

October 20, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0317-000-000
Brand name (generic)	Imbruvica (ibrutinib)
Indication(s)	Chronic lymphocytic leukemia (CLL)
Organization	Leukemia & Lymphoma Society of Canada
Contact information[a]	Name: Colleen McMillan, Advocacy Lead - [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
We agree that ibrutinib meets patients' need for more treatment options that are better tolerated with less toxicity and a favourable difference in PFS. We thank the committee for their support and for considering the significant benefit to patient 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 input previously, however we support the input provided by Lymphoma Canada regarding this treatment		

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.

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	*Colleen McMillan*
Position	*Advocacy Lead*
Date	*19-10-2023*
☒	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	PC0317-000
Brand name (generic)	Imbruvica (Ibrutinib)
Indication(s)	Ibrutinib in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion
Organization	Lymphoma Canada in collaboration with CLL Canada
Contact information[a]	Name: Gurjot Basra [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 overall recommendation that I+V be reimbursed but we do not agree with the condition on comparators Table 1, Item 7, which effectively undermines the recommendation for reimbursement, as we will explain below. CLL patients have expressed that it is important to them to have a choice of treatments that will be better tolerated and best suited to their personal clinical history. Overall, the patients we surveyed that did have experience with Ibrutinib + venetoclax found it was more effective in putting their CLL in remission with fewer side effects. Ibrutinib with venetoclax has addressed patient preferences with respect to choice and fewer side effects as well as longer progression free survival. Additionally, in comparison to existing treatments such as obinutuzumab, which requires intravenous administration and frequent hospital visits, and BTK inhibitors which are taken indefinitely, I+V offers the benefits of an oral therapy which is time-limited. This would be especially beneficial for those living in rural areas, who can not take time off work or have family responsibilities and is a cost saving measure for the health care system.		
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? As noted throughout our first submission, our input is a collaboration by Lymphoma Canada with CLL Canada.		
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. The reasons for the recommendation are clearly stated, however there are a few contradictions in the report. For example, in Table 2, V+O is listed as a funded comparator, however, the background section states that V+O "is not reimbursed publicly".		
	Yes	☐

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	No	☒

If not, please provide details regarding the information that requires clarification.
Reimbursement condition 7 states that "I+V should be negotiated so that it does not exceed the drug program cost of treatment with the least costly comparator reimbursed for the treatment of CLL". Looking at the implementation guidance, the comparators include BR and FCR and even C+O. The data is clear demonstrating limited efficacy for BR and C+O for CLL patients compared to BTKi and BCL2 treatments. In terms of FCR, despite its effectiveness in CLL patients with mutated IGHV, it is being used less and less as it poses the significant risk of a secondary cancers as well as prolonged immunosuppresion and myelosuppresion. Further, it is well established that remissions are short in patients who are given FCR and have an unmutated IGHV. FCR is only recommended in patients with mutated IGHV, therefore FCR is not necessarily a good comparator for patients with unmutated IGHV. CLL patients with unmutated IGHV should be considered Fludarabine ineligible in the definitions in the Economic Evidence table on page 18. These considerations guide clinical practice and result in the rapidly diminishing use of chemo-immunotherapy in favour of novel agents (BTKi &BCL2i)

Comparators to BTKi and BCL2 would be more appropriate and would better reflect actual clinical practice.

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.
The reimbursement conditions are clearly stated, however, the rationale for I+V being priced to match that of the least expensive comparator is limited to the fact that C+O, BR, and FCR are also fixed dose regimens. The draft recommendation provides a technical explanation for dismissing comparisons with newer treatments which a) we do not understand and b) is contrary to current clinical practice and standards of care. It does not take into consideration efficacy in that I+V may be more effective in resulting in remission in CLL patients with fewer side effects as expressed by the opinions of patients in our survey.
The responses from patients who received I+V treatment from our survey are highlighted below:

- "Seems to be a very good treatment with minimal side effects"
- "I have been in remission for 4 years following clinical trial treatment with ibrutinib and venetoclax at MD Anderson. Reached MRD negative after 9months treatment. Have been off all meds since 2019. My day-to-day life is not affected by CLL…."
- "highly recommend the I+V combo"
- "Seems to be a very good treatment with minimal side effects"
- "I think it was a very good first line treatment. 4 year from start of trial 96% still in remission. Financially cheaper than doing 4 years of monotherapy (2 year trial).

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

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	*Gurjot Basra*

Position	*Manager of Patient Programs, Research, and Advocacy*
Date	*October 20, 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.
Yes this feedback was completed in collaboration with CLL Canada.

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.
Yes, CLL Canada assisted in promotion of the original survey created by Lymphoma Canada

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**
Beigene	☐	☐	☐	☒
Astra Zeneca	☐	☐	☐	☒
Janssen	☐	☐	☐	☒

A. Collaborating Patient Group Information

Name	*Raymond Vles*
Position	*Board Chair*
Date	*October 20, 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.

1. 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**
Beigene	☐	☐	☒	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0317
Brand name (generic)	Imbruvica (Ibrutinib)
Indication(s)	Imbruvica with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion.
Organization	Ontario Health (CCO) 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. The Heme DAC would like to include SLL as an indication.		

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. The Heme DAC would like a retreatment option of ibrutinib and venetoclax. An addition of venetoclax to patients already on ibrutinib can be considered in selected patients.		
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 • *Add additional (as required)*		

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	

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0317
Name of the drug and Indication(s)	Ibrutinib in combination with venetoclax for the treatment of adult patients with previously untreated CLL including those with 17p deletion
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 Initiation (p. 4): PAG asked if there can be a statement on SLL similar to what was done for zanubrutinib. Health Canada indication did not include SLL. pERC acknowledged that jurisdictions could consider extending reimbursement to SLL, similar to what is already being reimbursed for BTKi and venetoclax-based regimens. A statement can be added to the Discussion or the DPI table.

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. The algorithm will need to be updated (rapid algorithm)
2. Please specify other implementation questions or issues that should be addressed by CADTH
Under Considerations for initiation of therapy (p. 9), PAG asked for more clarity on the protocol for retreatment. The CAPTIVATE study gave specific details: “After completion of the FD regimen, patients who subsequently had confirmed progressive disease (PD) by iwCLL criteria could be retreated with single-agent ibrutinib until PD or unacceptable toxicity. For patients who had PD>2 years after completion of the FD regimen, retreatment with the FD ibrutinib plus venetoclax regimen could be considered.” If pERC does not support continuing the ibrutinib after completion of the regimen if there was confirmed progressive (given only a handful of patients received single agent ibrutinib retreatment), PAG suggests adding a statement in the DPI table acknowledging that although this is in the protocol, there is insufficient evidence to support the continuation of single agent ibrutinib.
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	PC0317 Imbruvica
Brand name (generic)	IMBRUVICA® (Ibrutinib)
Indication(s)	IMBRUVICA® with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion
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 GLOW and CAPTIVATE, and is satisfied with the recognition of the added clinical value of I+V as a well tolerated targeted oral fixed duration therapy.

Janssen disagrees with CADTH's assessment that the pharmacoeconomic model was inadequate for decision making. The Sponsor's position remains that the methodological approach leveraged in the submitted model, was robust, valid, and sufficient to assess the cost-effectiveness of I+V versus pertinent comparators. Of note, an identical model structure was submitted to National Institute for Health and Care Excellence (NICE) and the model structure was assessed as adequate for decision making.

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.