CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

zanubrutinib (Brukinsa)

BeiGene (Canada) ULC

Indication: Waldenström's macroglobulinemia

November 18, 2021

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0248-000
Brand name (generic)	Brukinsa (zanubrutinib)
Indication(s)	For the treatment of patients with Waldenström's macroglobulinemia (WM)
Organization	Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Tom Kouroukis Email: [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.		

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 in the input, OH-CCO Hem DAC feels that the unfit treatment-naïve population (as per the ASPEN trial) should be included in the 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.

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 secretariat support to the DAC.		
3. Did you receive help from outside your clincian 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	

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
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 4	
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 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 Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0248
Name of the drug and Indication(s)	Zanubrutinib for Waldenström'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
None.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
In Table 3. Responses to Questions from the Drug Programs, under the heading "Relevant comparators, "PAG is requesting the following revision: "However, pERC also recognized the current widespread use of ibrutinib in Canada through *compassionate* access programs and therefore considered it a relevant treatment comparator." In Table 3. Responses to Questions from the Drug Programs, under the heading "System and economic issues, "PAG is requesting deleting the following text: "The drug plans noted the following: • The submitted BIA includes ibrutinib which is not publicly funded in Canada for WM. This may affect the BIA. • Presence of confidential negotiated prices is not applicable to ibrutinib as this agent is not publicly funded for WM." "pERC acknowledged that ibrutinib was not included in the budget impact estimate and that publicly listed prices for generics were used where available."

PAG is requesting that "pCPA" be omitted from the following the text: • Confidential negotiated price exists for biosimilar rituximab (pCPA) and rituximab SC. In the Clinical Evidence section under the heading "Critical Appraisal", PAG is requesting the following revision, "The most relevant *public funded* comparators for WM in Canadian jurisdictions include rituximab-based chemotherapy for treatment-naïve patients and relapsed disease."
b) Reimbursement conditions and related reasons
None.
c) Implementation guidance
None.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0248-000
Brand name (generic)	Zanubrutinib (Brukinsa)
Indication(s)	For the treatment of patients with Waldenström's macroglobulinemia (WM)
Organization	Lymphoma Canada, Canadian Organization for Rare Disorders (CORD)
Contact information[a]	Name: Kaitlyn Beyfuss-Laski, [redacted]

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

Zanubrutinib addresses an unmet need for Canadian WM patients and Lymphoma Canada and the Canadian Organization for Rare Disorders are in agreement with the recommendation for zanubrutinib to be reimbursed for this indication.

However, the joint organizations have reviewed the draft recommendation and request for modification to the listed reimbursement criteria:

1. **For section 3.1 of Table 1 (page 4)** – Zanubrutinib should not be prohibited for patients who have received prior exposure to a BTK inhibitor. This is specifically related to ongoing trials that provide a limited time use of a BTK inhibitor treatment in a certain line of treatment, thus not requiring discontinuation contingent on progression on a BTKi. Therefore, this section should be modified to "Prior progression on a BTK inhibitor" to not exclude those patients enrolled in a trial that stabilized disease or their disease responded to treatment, but required stopping the therapy due to reaching the required time limit of use on the trial.
2. **For section 4.1 of Table 1 (page 4)** → Review of the frequency of blood work is requested to be at the regular frequency that other BTK inhibitors require. Though we understand that blood work at an increased frequency is required to monitor disease response within a clinical trial, this may not be applicable or feasible in the real-world environment. The benefit for a patient of receiving an oral therapy is to limit the requirement to attend the hospital or clinic to receive treatment. However, with the frequency that blood work is required (i.e. every month), this is similar to what would be required for a patient receiving intravenous therapy or in a clinical trial. Especially with the current COVID-19 pandemic environment, monthly blood work may expose patients to additional risk while on therapy, and therefore should not be a strict condition that can prohibit use if not met for patient safety reasons. Frequency of blood work monitoring should be similar to the requirement/frequency used for other BTK inhibitors and should be at the discretion of the treating physician.
3. **For section 7 of Table 1 (page 4)** → It is important to note that though head-to-head trials indicate ibrutinib as the comparator, ibrutinib is only accessible through compassionate access, and therefore does not have an associated comparative pricing.
4. **For section 8 of Table 1 (page 4)** → Feasibility of adoption should be addressed for the therapy but not at the expense of the patient population. Access to this therapy should be made as early as possible for the eligible patient population with limited to no alternative treatment options in the relapsed/refractory setting and adoption discussions should be made rapidly.

Expert committee consideration of the stakeholder input		
	Yes	☐

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

LC and CORD agree that patient feedback was taken into consideration, acknowledging the needs of WM patients including treatment options that provide longer remission and survival and improved quality of life with fewer side effects.

However, it is important to note that in the Stakeholder Input (Patient Input section, paragraph 2) summary, no detail was included on the valuable input provided by 22 patients that received Zanubrutinib therapy; detail was only provided on the general WM experience. Important key highlights of the benefits of this therapy based on patient feedback that should be included in this summary are as follows:

- The majority of patients found some to all of their WM symptoms were managed by Zanubrutinib, with only 9% not experiencing symptom relief. Symptom relief and management included reduced fatigue (68%), night sweats (32%), shortness of breath (27%) and enlarged lymph nodes/abdomen (23%).
- None of the 22 patients that responded had to stop taking Zanubrutinib because of the side effects experienced, therefore indicating a tolerable side effect profile.
- Related to side effects and treatment administration, this did not negatively impact patients' quality of life, and instead had a trend towards a positive impact for their ability to continue with their daily activities, relationships, and employment.
- In comparison to patients that received other treatments, patients noted that Zanubrutinib had less side effects (64%), did not impact quality of life to the same extent as past treatments (36%), and had a better and faster response rate (41%) compared to previous treatments.
- 95% of patients responded they had a good to excellent experience with the therapy and mentioned they would take this treatment option again if recommended by their doctor and would also recommend it to other patients.

Clarity of the draft recommendation

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

The reasons for the recommendation are clearly stated and supported by data from the ASPEN clinical trial, patient group feedback, and clinician feedback.

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

Feasibility and implementation are related primarily to pricing as articulated in the draft recommendation, with a suggestion of up to a 93% reduction in pricing. This vast requirement for pricing reduction may contribute to a large barrier to access and delay. It is therefore recommended that a more in-depth population analysis be performed as to the number of WM patients in Canada and the number of patients in the relapsed/refractory setting eligible for BTKi therapy, as well as a systematic review for average length of administration of a BTK inhibitor for lymphoma patients, to better determine a more general pricing impact and then provide a better suggestion for a range for pricing reduction.

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

The reimbursement conditions are stated with rationale for the conditions provided. Suggestions for improvements are provided in section 1 and 4 of this document.

Greater clarification and input are required as to the reason for why Zanubrutinib is only approved for reimbursement for relapsed/refractory patients and not for the frontline treatment of WM patients, as this is not clearly outlined and both data and patient feedback is provided for TN WM patients and their experience with this therapy.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

A. Patient Group Information	
Name	*Kaitlyn Beyfuss-Laski*
Position	*Manager of Patient Programs, Research & Advocacy, Lymphoma Canada*
Date	*10-Nov-2021*
☒	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	☒
Feedback input was provided by CORD.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☒
CORD and WMFC were involved in the collection and analysis of information used in the feedback.		

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
n/a	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0248-000
Brand name (generic)	Zanubrutinib (Brukinsa)
Indication(s)	For the treatment of patients with Waldenstrom's macroglobulinemia
Organization	Waldenstrom's Macroglobulinemia Foundation of Canada
Contact information[a]	Name:Joseph Lewicki, [redacted]

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

The Waldenstrom's Macroglobulinemia Foundation of Canada (WMFC) wishes to thank the Reimbursement Recommendation review committee for this opportunity to provide feedback before their final recommendation is released. We are a WM patient group, organized and run by volunteers. We fund patient support group meetings, and organize national forums where patients can listen to, and interact with, internationally renowned WM experts. We donate approximately 100,000$ per year to WM research. And we are currently in the final stages of organizing an educational WM Grand Rounds for Canadian haematologists, delivered by the Bing Center for Waldenstrom's Macroglobulinemia, part of the Dana Faber Cancer Institute (DFCI) in Boston. DFCI is arranging for these grand rounds to be accredited in Canada so that haematologists can earn credits towards their regular certification reviews. We are a very focused and active organization.

While we agree with the recommendation that zanubrutinib should be funded, we would like to go on record to stipulate where we are in complete agreement and where we disagree with the conditions and why we do so. Here is the position of the WMFC:

: We agree with the CADTH recommendation to not recommend zanubrutinib as a first line therapy for WM. The WMFC sees no need for the use of zanubrutinib as a first line therapy. The combination of bendamustine and rituximab (BR), possibly along with maintenance rituximab, is both therapeutically effective and very cost effective. We anticipate BR being the front line treatment for years to come.

: Further, the WMFC believes that current Canadian standards for treatment of relapse in WM, using a repeat of BR, or switching to the combination of bortezomib, rituximab and dexamethasone (BoR-DR), is clinically and financially acceptable, given current evidence. We are very aware of the financial pressures placed on provincial medical systems. These treatments should continue until they are no longer effective.

: Our concern is what happens when BR and BoR-DR are no longer effective. And that is the issue that we wish to address through feedback to the draft CADTH Reimbursement Recommendation.

Where the WMFC disagrees with the draft report:

: We recommend that you change the wording of section 3.1 of Table 1 (pg. 4) from "Prior exposure to a BTK inhibitor" to "Progression while on a previous BTK inhibitor". 69 WM patients are to be

enrolled in a pan Canadian WM PH II trial of BR-acalabrutiinib (BRAWM trial). Acalabrutinib will only be administered for one year. The trial is up and running from coast to coast.

: We believe that medical science is not driven forward by consensus but rather by scientific challenge. We draw your attention to the line in your draft Reimbursement Recommendation under Rationale for the Recommendations, (pg. 3 – last paragraph), which states, **"There was no reliable evidence to quantify any additional benefit provided by zanubrutinib in R/R and treatment naïve patients with WM relative to funded comparators"**. To state, as the quoted line does, that there is no quantifiable, additional benefit gained by using zanubrutinib in R/R is factually incorrect. CADTH is assuming that it can compare zanubrutinib to BR or BoR-DR in the relapse setting. But current Canadian practice, supported by the WMFC, is to use BR and DoR-DR until there is no longer benefit in doing so. If BR and BoR-DR can no longer confer a benefit in an R/R setting, they should not be used as a comparator to zanubrutinib.

: We wish to point out an omission in the draft Reimbursement Recommendation that is critical to understanding the importance of zanubrutinib. This is not new evidence. Quoting from the draft Reimbursement Recommendation (pg. 7) "Sources of Information Used by the Committee – A review of 1 of randomized phase 3 trial in patients with WM", the ASPEN trial. It is data from the ASPEN trial that was edited out and it is therefore not new data. The omission is the overall response rate (ORR) of zanubrutinib in a relapsed or refractory setting in WM.

: The ASPEN trial data, used and extensively quoted by CADTH, states clearly that the overall response rate in WM R/R is 94% with a further 4% exhibiting stable disease. There is no R/R comparator that would be available that comes anywhere near those numbers except for alternate BTK inhibitors. The full breakdown of the ASPEN report data, which CADTH edited for the draft Reimbursement Recommendation, is ORR 94%, CR 0%, VGPR 29%, PR 49%, MR 16% and stable disease 4% (Table 2 in the Aspen report). This is not new data because CADTH used the trial data in formulating the reimbursement recommendation. It was wrong of CADTH to exclude the overall rate of response and just include the VGPR at 29%. Why was the ORR of 94% in relapsed or refractory WM removed? The ORR was not the primary endpoint of the trial but that is irrelevant. An ORR of 94% is an exceedingly important number when evaluating the efficacy of zanubrutinib in WM R/R.

: The WMFC would hope to see the final recommendation include the name of a comparator that can be used instead of zanubrutinib and that you would include response rates, progression free survival rates and costs for both treatments. Again, please note, the WMFC, and current Canadian practice, have already agreed that the use of steroids, alkylating agents, bortezomib and rituximab are warranted until they are no longer effective. This should invalidate BR or BoR-DR as a comparator.

: Why is CADTH referencing the International Workshop in Waldenstrom's Macroglobullinemia-7 (IWWM-7 2014) when IWWM-10 (2020) was available? Of note, IWWM-10 reports on the WM PH III double blind placebo iNNOVATE trial, consisting of ibrutinib and rituximab vs placebo and rituximab. We have very deep concerns about pERC CADTH accessing ancient internationally agreed upon recommendations while ignoring modern internationally agreed upon recommendations.

: We would like to quote again from the draft Reimbursement Recommendation, under Rationale for the Recommendation, (pg. 3 – 2nd paragraph), "**Ibrutinib (obtained through compassionate access) has become a de facto standard of treatment in Canada for patients in the R/R setting"**. We wish to point out that patient access to BTK inhibitors is divided between compassionate access and private insurance held by advantaged WM patients. When compassionate access programs end, and they will, WM patients will be left with a two tier health care system. The clinical effectiveness of BTK inhibitors for WM R/R is exactly why Canadian

haematologists are accessing BTK inhibitors for their R/R WM patients. No other treatment comes close. PH III data used by CADTH recommendations for ibrutinib in CLL and zanubrutinib in WM, show that BTK inhibitors are as effective in WM as they are in CLL. Again, that is PH III data used by pERC and CADTH.

: Please note, we do not anticipate a future WM PH III trial of a BTK vs BR in the treatment of naïve patients as BR has comparable rates of effectiveness and a huge cost advantage in the treatment of naïve WM patients. Nor, for the same reasons, do we anticipate a trial of zanubrutinib vs BR or BoR-DR in a relapse setting. The concern of the WMFC is limited to what happens when steroids, alkylating agents, rituximab and bortezomib are no longer effective.

: Quoting from the draft CADTH Reimbursement Recommendation, under Discussion Points (pg. 5 first line), WM has "**an incidence in Canada of 1 in 200,000 people per year**". That is 10% the incidence of CLL. With so few patients, It is extremely difficult to run PH III trials in WM in a rapidly changing pharmaceutical environment, hence the importance of using IWWM-10. The WMFC would like to emphasize that ours is a rare cancer. Clinicians base their selection of treatment regimens largely on PH II trials, out of necessity. The number of WM patients who would require access to BTK inhibitors is very small. But for that small group, BTK inhibitors can be critical to a longer and better quality of life. There is no equivalent to BTK inhibitors after the failure of BR and BoR-DR.

The WMFC offers the following recommendation to CADTH:

: The WMFC recommends funding approval for zanubrutinib when rituximab based therapies like BR and BoR-DR are no longer effective. This should be subject to provincial price negotiations with the manufacturer, which could be based on provincial guidelines for acceptable costs for quality of life per annum. With ibrutinib, zanubrutinib and acalabrutinib now being used by WM patients in Canada, and with pirtobrutinib on the horizon, there is plenty of room for market forces to affect price negotiations.

Thank you for your consideration of this feedback.

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. But CADTH has unwarranted assumptions in the draft Reimbursement Recommendation.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
		☐
Yes, but we challenge the accuracy of your comparator analogy. And again, the overall response rate in the ASPEN trial was not included in the draft CADTH Reimbursement Recommendation.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?		☐
	No	☐
We request that CADTH bring clarity to the "comparator" issue.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
		☐

The rationale was clear but CADTH failed to identify a treatment, after BR and BoR-DR fail, that comes anywhere near Zanubrutinib's 94% response rate in the ASPEN 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	*Joseph William Lewicki*
Position	*WMFC Board Member - science*
Date	*(15-11-2021)*
☐	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. ***Certified by Joseph Lewicki***

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
		☐
No help was provided.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
		☐
No help was provided.		

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	☐
		☐

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 $50,000**
Janssen 4,000$	☐	☐	☐	☐
Beigene 15,000$	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0248-000
Brand name (generic)	BRUKINSA (zanubrutinib)
Indication(s)	Waldenström's Macroglobulinemia
Organization	BeiGene (Canada) ULC
Contact information[a]	Name: [redacted]

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

BeiGene supports the recommendation that zanubrutinib be reimbursed for the treatment of patients with relapsed or refractory (R/R) Waldenström's macroglobulinemia (WM) as this is in line with Health Canada's approved label.

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	☐

We agree the recommendation reflects stakeholder input calling for access to zanubrutinib.

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

Yes, the reasons for the recommendations for R/R WM patients reflect product evidence and current standard of practice.

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

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

BeiGene is pleased that pCODR (CADTH) has recognized the need for Brukinsa (zanubrutinib) for the treatment of adult patients with Waldenström's Macroglobulinemia (WM) in its recommendation to list with conditions. BeiGene believes that the reimbursement conditions clearly state the rationale for the conditions as provided in the recommendation, subject to some additional clarity for two conditions, as follows:

(1) Table 1. Reimbursement Conditions, Initiation, Exclusion 3.3 "active cardiovascular disease" (page 4): BeiGene acknowledges that the criteria "active cardiovascular disease" was taken

directly from the inclusion/exclusion criteria from our clinical development program, however, without context, it may lead to confusion in the implementation of the criteria itself.

Cardiovascular disease, in broad terms, is a common condition of elderly patients and especially those with WM. **BeiGene respectfully requests that the reference to exclusion criteria 3.3 be removed in recognition that Canadian clinicians are well experienced in the use of Bruton Tyrosine Kinase Inhibitors (BTKi's) and have been using a first generation BTKI (ibrutinib) without such criteria, which has a less favorable CV toxicity profile**.[i, ii, iii]

If removing the condition is not acceptable, then clarification of the active cardiovascular disease is requested, with the following suggested wording that may be derived from the Clinical Review Report (p.28, Table 4, Exclusion criteria)

"Currently active, clinically significant cardiovascular disease (e.g., uncontrolled arrhythmia, congestive heart failure) or treatment with warfarin or another vitamin K antagonist, or history of myocardial infarction within 6 months …"

(2) Table 1, Reimbursement Conditions, Pricing, 7, page 4: BeiGene commends pCODR / CADTH for recognizing the unmet need for Brukinsa for patients with WM. With respect to pricing, BeiGene understands the need to compare to other treatments, however, we would suggest comparisons should only be with treatments that are likely to be used by clinicians today. It is extremely unlikely that clinicians (as per the chart review data shared as part of the submission) to use a Bor-DR regimen. Moreover, we know, based on guidelines that Bor-DR is not available widely (e.g., only in Saskatchewan and Quebec) and is difficult to access unless you regularly treat myeloma. Using Bor-DR as a price comparison for the unmet need zanubrutinib addresses for R/R WM patients would appear to not be reflective of current Canadian clinical practice.

While it is true that ibrutinib is currently not widely reimbursed on public plans, it is acknowledged by pERC that ibrutinib is considered the de facto standard of treatment and it is accessed by WM patients through case-by-case reimbursement on some participating plans or through a temporary compassionate access program from the manufacturer. In addition, there is widespread paid access through the patient d'exception measure in Quebec.

Throughout the draft guidelines, pCODR / CADTH and pERC align that ibrutinib, a first generation BTKi, is the *de facto standard of treatment* (Page 3, Rationale for Recommendation, paragraph 2):

> *"…based on input from the clinical experts and patients, ibrutinib and zanubrutinib are the most frequently used treatments in the R/R setting after failure of chemoimmunotherapy." (Page 5, Discussion points)*
> *"…"pERC recognized the current widespread use of ibrutinib in Canadian clinical practice through temporary compassionate access programs and agreed the frequency of its use deemed it a relevant treatment comparator." (Page 6, paragraph 2)*

Furthermore, the draft recommendation acknowledged:

> *"…According to the clinical experts consulted by CADTH, there is no standard of care therapy for R/R WM as few patients are eligible for retreatment with chemoimmunotherapy…" (Page 5, Discussion points)*
> *"…there is **a significant unmet need** for more treatment options in WM, most notably for patients with R/R WM for whom there is presently no clear standard of care regimen and*

retreatment with chemoimmunotherapy is of limited efficacy." (Page 3, Rationale for Recommendation, paragraph 2)

BeiGene respectfully requests that the language in the recommendation be amended to acknowledge the alignment in the clinical review that ibrutinib is the comparator, more specifically for the following:

> *"Zanubrutinib 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 R/R WM*."(Page 4, Table 1, Pricing. Bullet 7)

should be reworded as follows:

> "Zanubrutinib should be negotiated so that *a reduction in the price of zanubrutinib would be required to improve cost-effectiveness to an acceptable level* for the treatment of R/R WM."

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

References:

[i] Ahn IE. Cardiovascular adverse events of ibrutinib. Blood. 2019;134(22):1881-2

[ii] Dickerson T, Wiczer T, Waller A, Philippon J, Porter K, Haddad D, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. Blood. 2019;134(22):1919-28.

[iii] Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. Blood. 2020;136(18):2038-50