Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

venetoclax (Venclexta)

(AbbVie Corporation)

Indication: Venclexta in combination with ibrutinib, is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.

March 3, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CDA-AMC and do not necessarily represent or reflect the views of CDA-AMC. No endorsement by CDA-AMC is intended or should be inferred.

By filing with CDA-AMC, the submitting organization or individual agrees to the full disclosure of the information. CDA-AMC does not edit the content of the submissions received.

CDA-AMC 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 group and all conflicts of interest information from individuals who contributed to the

CADTH

CADTH Reimbursement Review
Patient Input Template

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Venetoclax (Venclexta)

Indication: Venclexta, in combination with ibrutinib, is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Name of Patient Group: Lymphoma Canada

Author of Submission: Gurjot Basra, Manager of Patient Programs, Research, and Advocacy

1. About Your Patient Group

Lymphoma Canada is a national Canadian registered charity whose mission it is to empower patients and the lymphoma community through education, support, advocacy, and research. Based out of Mississauga (ON), we collaborate with patients, caregivers, healthcare professionals, and other organizations and stakeholders, to promote early detection, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma, and work together to find a cure. Resources are provided in both English and French. www.lymphoma.ca

2. Information Gathering

The data presented in this submission was collected from an online anonymous patient survey, created and promoted by Lymphoma Canada (LC) available from January 31st to March 2nd, 2025. The link was promoted via e-mail to patients registered in the LC national emailing list and made available via social media outlets, including Twitter, Instagram, and Facebook accounts. The survey had a combination of multiple choice, rating, and open-ended questions. Skipping logic was built into the survey so that respondents were asked questions only relevant to them. Open-ended responses were noted in this report verbatim, to provide a deeper understanding of patient perspectives. 82 responses were collected amongst those who had Mantle Cell Lymphoma (MCL). Information from this survey was used to identify the main areas of concern for patients with MCL, with 5 confirmed responses for experience with the therapy under review, Venetoclax + Ibrutinib (V+I). Of the five patients who received this therapy in second line, 3 were male and 2 were female, ages ranging from 35-84. 3 of these patients were from Canada, and 2 were from the United States.

Please see tables 1-4 below for demographic and relevant information of all survey respondents. The majority of patients lived in Canada (74%), between the age of 65 and 74 (36%) or 75 and 84 (23%), female or male (49% for both), and were diagnosed 3-5 years ago (27%), 9-10 years ago or greater (24%), or 1-2 years ago (22%).

Table 1: Country of respondents from Lymphoma Canada survey

Respondents	CAN	USA	Australia	United kingdom	Skipped	Total
Patients with Mantle Cell Lymphoma	39	12	1	1	29	82

Table 2: Age range of respondents from Lymphoma Canada survey

Respondents	Age (years old)									
	18-24	25-34	35-54	45-54	55-64	65-74	75-84	Over 90	Skipped	Total
Patients with Mantle Cell Lymphoma	0	1	2	10	9	19	12	0	29	82

Table 3: Gender of respondents from Lymphoma Canada survey

Respondents	Gender				
	Female	Male	Prefer Not to Answer	Skipped	Total
Patients with Mantle Cell Lymphoma	26	26	1	29	82

Table 4: Number of years ago respondents were diagnosed with Mantle Cell Lymphoma

Respondents	Years						
	<1	1-2	3-5	5-8	9-10	Skipped	Total
Patients with Mantle Cell Lymphoma	8	15	18	10	16	15	82

3. Disease Experience

At Diagnosis

Through Lymphoma Canada's online survey, patients were asked to rate a list of physical symptoms on a scale of 1 (no impact) to 5 (significant impact) in regards to their quality of life upon diagnosis. The most common reported symptoms rated as a four or five were: Fatigue/lack of energy (33%), enlarged lymph nodes (27%), indigestion, abdominal pain or bloating (22%), night sweats (22%), weight loss (21%), and high white blood cell counts (leukocytosis) (18%).

Respondents of the survey were also asked to select from a list of psychosocial impacts they experienced when diagnosed with MCL. Of the 67 patients that responded to this survey question, 72% experienced stress of diagnosis, 70% experienced anxiety, 64% had fear of progression, 39% experienced difficulty sleeping. Other challenges included fear of not being able to continue daily activities (28%), challenges with the frequency of healthcare appointments (27%), fear of not being able to attend school/work (25%), depression (25%), and problems concentrating (24%).

When asked to provide additional details about the challenges faced during diagnosis, several patients commented on difficult symptoms and increased anxiety/fears:

- "Searching for information online only added to the stress since it was not positive in the outcomes"
- "Had to take stress leave from work"
- "I am 42 so the diagnosis was shocking- it was difficult to understand what my prognosis might be. Lots of worry around limited lines of treatment available"
- "Frustration at the lack of effective treatments and lack of a cure. Knowing that the disease will recur with whatever treatment I undertook."
- "The diagnosis was a shock as not a cancer one hears about. Information from Drs. and support from wife was very important"

Current Quality of Life

To understand the factors which currently impact patients with Mantle Cell Lymphoma, respondents were asked a similar style of questions from the diagnosis section of the survey. On a scale of 1 (no impact) to 5 (significant impact), 28% of patients rated fatigue/lack of energy as a 4 or 5, and 15% of patients rated low white blood cell counts (neutropenia) as a 4 or 5.

Patients also indicated they recently experienced mental health challenges such as fear of progression/relapse (74%), stress of having cancer (41%), difficulty sleeping (38%), and anxiety/worry (31%).

Daily Activities

Regarding day-to-day activities, patients with Mantle Cell Lymphoma rated several factors on a scale of 1 (no impact) to 5 (very significant impact) which impacted their daily life. Of the 61 respondents who completed the question, the ability to travel (38%), ability to work, school and volunteer (28%), ability to spend time with

family and friends (20%), and ability to exercise (18%) were rated as a 4 or higher. Many patients left comments in this section and a selection of quotes are included below:

- “Struggling probably more in mental health than physical health which is stopping me returning to work”
- “I have young children- when they have colds and illnesses I have to isolate from them to prevent becoming ill. I can’t work my usual job (I’m a firefighter). At the moment i receive sick pay but that will finish soon and its likely i will not be able to return for at least another year as i am handing an auto SCT. My wife has had to do everything whilst working and getting me to appointments.”
- “Because of my weak immune system, routine daily outings (ex: grocery shopping, appointments) and social occasions are a big risk to my health. A simple cold will last for 3 months or turn into a pneumonia. I have to be very careful about what I eat so I almost never eat out at restaurants. Everything must be well-cooked, well washed, pasteurized, etc. Socially, my family, friends and colleagues are worried about infecting me with a cold, the flu, etc. Socially, it can be very isolating, especially in the winter.”
- “Lost the interest to meet friends or attend any social group.”
- “Having to be always aware of a compromised immune system”
- “Immunosuppression from MCL maintenance and clinical trial of Acalabrutnib created a secondary cancer - mouth cancer, which is severely impacting my day-to-day life.”
- “Our travel away from home is dictated by the schedule of my maintenance treatments every 3 months for the next 2 years. Coming off the prednisone after 10 months of high doses daily was a very big adjustment to my joints and muscles. It has taken several months to begin to feel more normal in my daily activities and to start to build back some muscle strength. Physiotherapy has helped me. I have struggled with a sensitive stomach and now need to avoid certain foods.”

Summary

For many patients, to live with MCL means living with fatigue/lack of energy, abdominal issues, anxiety/stress, and a fear of progression/relapse, all of which have a significant impact on a person’s quality of life.

4. Experiences With Currently Available Treatments

Patients who completed the Lymphoma Canada survey were asked if they required immediate treatment following their diagnosis or if they were on Watch and Wait for a period of time (> 1 month) before starting treatment. 64% of patients required immediate treatment while 36% were on watch and wait.

Patients were also asked how many lines of treatment they received to treat their Mantle Cell Lymphoma. The majority of patients indicated they received 1 (56%) or 3+ (22%) lines of treatment, see Table 6.

Table 6: Number of lines of therapy survey respondents received

Respondents	Have not yet received therapy	**1**	2	**3+**	**Skipped**	**Total**
Patients with Large B-cell lymphoma	4	33	9	13	23	82

In the front-line setting, 35% of patients received BR (Bendamustine, Rituximab), 25% of patients received R-CHOP chemotherapy (rituximab,cyclophosphamide, doxorubicin, vincristine and prednisone), and 12% received R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) or BEAM Therapy (carmustine (BiCNU) or lomustine (CCNU), etoposide, cytarabine (Ara-C, cytosine arabinoside), and melphalan). In second line or beyond, 29% of patients received a stem cell transplant (i.e. ASCT) and 15% of patients received treatment with BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib).

These patients were asked: “How satisfied were you with the number of treatment options available to you for your lymphoma?”. 78% of patients indicated they were very satisfied or satisfied with their frontline treatment options. While 27% of survey respondents gave the same rating in second-line treatment, and 13% with their third-line treatment options. This indicates patients are less pleased with their treatment options in second- and third-line settings and more treatment options need to be made available.

When asked which side effects were the most difficult to tolerate many patients indicated fatigue, nausea, insomnia, loss of appetite/weight loss, hair loss, constipation, joint pain, bodily aches and pain, neuropathy, mouth sores, muscle weakness, and diarrhea. Some patient remarks to this question:

- “Fatigue was extremely difficult to overcome”
- “I experienced lots of nausea, then I crashed hours after the stem cell transplant and was in crisis in ICU for several days. It took months to get my gut functioning again.”
- “Fatigue, exercise intolerance, immunosuppression”
- “Fever every month with BR”
- “15 days of radiation left me in bed for a month unable to eat.”

Of the 48 patients who provided information about their ability to access their MCL treatment, 10% of patients had some difficulty or a lot of difficulty. If patients were not able to access treatment, the main reasons were because the treatment was not available/they could not access the treatment at their local cancer center (11%), or because they lived in a community without a cancer center (3%). The most common

financial implications reported for treatment for MCL were absence from work (38%), travelling costs (34%), drug costs (23%), and supplementary drug costs for side effects (15%).

Here are some comments from patients in terms of difficulties regarding access to treatment in Canada as well as financial implications:

- "Initially I travelled to a centre twice monthly for 6 cycles to a centre 200 km from my home due to space availability. However, the maintenance program was delivered at my local cancer centre."
- " The Acalabrutinib trial was not available locally"
- "The most difficult aspect was paying for parking at the hospital for treatment. I have had many, many appointments that cost over $20 for parking, and cannot claim it on my taxes."
- "Distance was the main difficulty"
- "I lost my job and due to absence was unable to participate in competitions for other positions in my workplace."

Summary of the Current Available Therapies

- Side effects of treatment and their impacts on the patient's quality of life remain a significant issue for survey respondents and based on satisfaction measures, more than half of respondents indicated the need for more options for 2nd and 3rd line treatment for MCL.

5. Improved Outcomes

MCL patients which completed the Lymphoma Canada survey were asked how important it was for a new drug to control/treat their Mantle Cell Lymphoma. MCL patients indicated factors such as longer disease remission (91%), longer survival (91%), improved quality of life to perform daily activities (79%), control disease symptoms (75%), and normalize blood counts (74%), were very important to them.

48 out of the 53 patients who responded (91%) indicated they would be willing to tolerate side effects to access new treatment options if side effects were not very severe and short term. 40 patients (76%) indicated choice is important to them (scored a 7 or higher out of 10) in deciding to take a drug based on known side effects and expected outcomes of treatment.

Patients were also asked, "When considering treatment for your lymphoma, how important is it for you to have the choice in deciding which drug to take based on how it is administered (e.g., oral (taken by mouth), subcutaneous (injection under the skin), infusion (administered via an IV, which may take a few hours or days), etc.)? Please rate from 1 (Not Important) to 10 (Extremely Important to have this choice)". Over 50% of patients indicated the importance in choice based on how the therapy is administered, providing ratings

between 7-10. V+I is an oral therapy, indicating how patients prioritize convenience and the ability to manage their treatment at home, avoiding the need for hospital visits and intravenous infusions, which can significantly improve their quality of life and overall treatment experience.

When participants were asked if there is currently a need for more therapy options for patients with Mantle Cell lymphoma, 46 patients (87%) answered “yes”.

Comments in regards to patient expectations for new therapies to manage lymphoma included:

- “It would be great to have a cure and be free from treatment and appointments!”
- “If I have a relapse I would like to know that there are several options to consider in consultation with my oncologist.”
- “I would like Health Canada to partner with their European and American counterparts to approve treatments more quickly so we’re not so far behind.”
- “Need to be able to access a range of different therapies which target MCL in different ways. Length of remission and quality of life is important. Burden of treatment is important and finding treatments which require limited contacts with hospital is important.”
- “Please find a first line treatment that is effective and provides a long-lasting remission. Please continue to support research that gives doctors and their patients options when a relapse occurs.”
- “I just hope that when I relapse there is or are treatment(s) that can help me cheat death for several more years.”
- “I will likely relapse at some point so I strongly support new therapies. Ideally treatment should have fewer side effects and allow for acceptable quality of life.”
- “I have my fingers crossed daily wondering what treatments will be available for me when relapse occurs and how effective they will be.”
- “I am expecting more of targeted therapies rather than chemotherapy drugs which have lot of side effects.”

Summary of Improved Outcomes

- MCL patients identified factors important for novel treatments, which included longer life span, longer remission, better quality of life and fewer side effects.
- A majority of patients believe it is very important to have choice in their treatment decision and a variety of treatment options to choose from.

6. Experience With Drug Under Review

From survey responses, 5 patients indicated they were treated with Venetoclax + Ibrutinib in the second line setting. These patients reside in Canada (3), and the United States (2). 1 patient was 35-44 years old, 1 patient was 45-54 years old, 2 patients were 55-64 years old, and 1 patient was 75-84 years old. 1 patient accessed this therapy as part of a clinical trial, 1 via private insurance, 1 through Medicare or public care, and 2 patients received this treatment through a compassionate access program (manufacturer company). In terms of the stage of their cancer journey, 1 patient is in new remission (less than 6 months), 3 patients have been in remission for 1-2 years following this therapy, and 1 patient relapsed after V+I treatment.

The main side effects reported included diarrhea (3 patients), low white blood cell count (neutropenia) (2 patients), and fatigue (2 patients). 1 patient experienced joint or muscle pain and 1 experienced constipation or bowel obstruction. Psychological impacts included anxiety/worry (3 patients), and fear of progression/relapse (2 patients).

In terms of overall experience with this therapy, 3 patients rated it as very good while 2 patients rated it as satisfactory, but all 5 said they would recommend it to other patients with MCL.

Comment shared by one of the respondents from the survey:

- "The treatment is by mouth, therefore no need for a central line and all the associated risks of a central venous catheter. There is no need to be hospitalised. There is no hair loss. In my case my disease relapsed after about 12 months but during those months, I was able to enjoy an extra year of life with my family, without the extreme toxicity and side effects of traditional chemotherapy. I believe that MCL patients should have access to this line of therapy."

Summary of Drug under Review

- The patients who had undergone therapy with venetoclax + ibrutinib experienced fewer side effects, primarily diarrhea and fatigue.
- All 5 patients who received this therapy would recommend the therapy to other MCL patients.

7. Companion Diagnostic Test

N/A

8. Anything Else?

Lymphoma Canada advocates for lymphoma patients to have access to innovative treatment options, such as venetoclax + ibrutinib, for mantle cell lymphoma (MCL). The availability of novel therapies provides patients with more personalized treatment choices, allowing them to work closely with their healthcare team to determine the best plan based on their individual needs and goals. For MCL patients, particularly those with relapsed or refractory disease, treatment options are essential. MCL is an aggressive lymphoma with a challenging prognosis, and many patients experience relapse after initial therapy. Ibrutinib and venetoclax offer a promising second-line+ treatment option, providing targeted therapies that can be taken orally, allowing patients to avoid the side effects of traditional chemotherapy, such as hair loss and prolonged hospitalizations. This combination therapy has been shown to improve outcomes in patients who have already received one or more prior therapies, offering a better quality of life with fewer toxicities.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie				X
AstraZeneca				X
Gilead				X
Novartis			X	
Roche		X		
Incyte			X	

BMS				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.

Name: Gurjot Basra
Position: Manager of Patient Programs, Research, and Advocacy -
Patient Group: Lymphoma Canada
Date: March 3, 2025

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0402-000
Generic Drug Name (Brand Name): Venetoclax (Venclexta)
Indication:
Manufacturer Requested Reimbursement Criteria:
Venclexta in combination with ibrutinib, is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.
Name of Clinician Group: Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee ("OH (CCO) Hem DAC")
Author of Submission: Dr. Tom Kouroukis and members of the OH (CCO) Hem DAC

1. About Your Clinician Group

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered via teleconference meeting.

3. Current Treatments and Treatment Goals

In relapsed/refractory (R/R) MCL, ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib (acalabrutinib, zanubrutnib, and pirtobrutinib are available via manufacturer compassionate program) or retreatment w/ rituximab-chemo or chemo alone (if rituximab refractory) are treatment options.

Other option include bortezomib-based treatment.

Brexucabtagene autoleucel is also available as a third line option.

Treatment goals – Increase survival, delay disease progression, symptom improvement, improve health-related quality of life.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Increase survival, delay disease progression, symptom improvement, improve health-related quality of life.

There are no curative therapies for R/R MCL.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Venetoclax-ibrutinib could potentially replace BTK inhibitor as alternative second line option given benefits in progression-free survival (PFS) and time to next treatment. This may also delay the need for third-line CAR-T.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The randomized study enrolled BTKi naïve patients; however, the OH-CCO Hem DAC suggests that patients who are not refractory to BTKi should have access to ibrutinib-ventoclax in the R/R setting because of limited treatment options.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Standard lymphoma response measures.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Discontinue if there is unacceptable toxicity or disease progression.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Outpatient setting (inpatient not needed with the ramp up).

6. Additional Information

N/A

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO PDRP provided secretariat function to the group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Tom Kouroukis
Position: Lead, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
Date: 27-02-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Christopher Cipkar
Position: Member, OH-CCO Hem DAC
Date: 27-02-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Rami El-Sharkaway
Position: Member, OH-CCO Hem DAC
Date: 27-02-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie	X			
The Leukemia & Lymphoma Society of Canada (sponsored talk)				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Jordan Herst
Position: Member, OH-CCO Hem DAC
Date: 27-02-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Selay Lam
Position: Member, OH-CCO Hem DAC
Date: 27-02-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie		X		
Janssen		X		
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Lee Mozessohn
Position: Member, OH-CCO Hem DAC
Date: 27-02-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Guillaume Richard-Carpentier
Position: Member, OH-CCO Hem DAC
Date: 27-02-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0402-000
Generic Drug Name (Brand Name): venetoclax
Indication: Venclexta in combination with ibrutinib, is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.
Name of Clinician Group: Lymphoma Canada Physician Group
Author of Submission: Dr. Mona Shafey, Dr. Pamela Skrabek, Dr. Carolyn Owen, Dr. Kerry Savage, Dr. Laurie Sehn

1. About Your Clinician Group

Lymphoma Canada is a national organization dedicated to research, education, and raising awareness to benefit patients with lymphoma across Canada. (Home - Lymphoma Canada)

2. Information Gathering

Published clinical trials for the treatment of relapsed/refractory mantle cell lymphoma were reviewed, with a focus on available phase III data, though phase II data was also considered. Available provincial guidelines were also reviewed for current treatment algorithms, as well as a review published in 2022 written by Canadian lymphoma experts across the country (Villa D, Kansara R, Lemieux C, Kuruvilla J. Updates in the treatment of mantle cell lymphoma: A Canadian expert framework. Can Hematol Today [Internet]. 2022 Dec. 14 [cited 2025 Feb. 11];1(S12):2–11. Available from: https://canadianhematologytoday.com/article/view/1-s12-villa_et_al).

3. Current Treatments and Treatment Goals

Frontline treatment of mantle cell lymphoma depends on patient characteristics (age and fitness) as well as disease biology. A small proportion of mantle cell lymphoma patients are considered indolent (usually low burden lymph nodes, leukemic presentation, with low Ki-67 and SOX11 negative) that can undergo observation for a time (average 1 year). Nearly all patients progress to warrant therapy, and therapy approaches are similar to classical MCL. Front line therapy in Canada currently consists of chemoimmunotherapy, with or without consolidation with high dose therapy (HDT) and autologous stem cell transplant (ASCT), followed by maintenance rituximab. Chemoimmunotherapy inductions are most commonly bendamustine-rituximab alone, bendamustine-rituximab alternating with rituximab-cytarabine, or RCHOP/RDHAP. HDT-ASCT is generally offered to patients age <65 who are fit for cellular therapy. The recent presentation of the Triangle Study demonstrated that the combination of ibrutinib + RCHOP/DHAP, followed with or without HDT-ASCT, was superior to that of RCHOP/DHAP/HDT-ASCT, and thus many centres are now considering this approach in the future but it is not currently a Canadian standard.

It is anticipated that all patients with MCL will relapse despite frontline treatment, with shorter PFS and OS in patients with high risk features (e.g. high risk MIPI, TP53-mutated, blastoid morphology). Standard second line treatment in Canada is indefinite ibrutinib monotherapy until progression. Second generation BTKis are not funded, but Zanubrutinib remains available on compassionate access for this indication thus is widely used to reduce the risk of toxicities associated with long-term use of ibrutinib. It is expected that patients will progress on BTKis, and for those that are fit for intensive treatment, CAR T therapy and even allogeneic stem cell transplantation may be options, but for the majority of patients, only palliative therapies remain, with agents such as bortezomib and

lenalidomide demonstrating some activity but with poor outcomes (<1 year PFS). Relapse after BTKi is an area of unmet need, as survival outcomes are poor in this setting with available treatments, and thus strategies that maximize the benefit of BTKi in combination with other agents (in this case venetoclax) in earlier lines of therapy would be beneficial for patients.

The goal of therapy for patients with mantle cell lymphoma is long-term PFS and OS, resolution of lymphoma-related symptoms and improvement in quality of life. Therapies that delay lymphoma progression are particularly important, since this disease cannot be cured with available treatments.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Patients with relapsed/refractory MCL have poor outcomes with current available therapies and this remains an area of unmet need. The original phase III study demonstrating superiority of ibrutinib over temsirolimus had an average PFS of 15 months, slightly longer if it was used in second line vs. subsequent lines of therapy, thus there is significant room for improving outcomes in this setting. CAR T therapy with brexu-cel is now funded in Canada, but access to CAR T remains a significant barrier in many jurisdictions since it is only available in specialized treatment centres, and is reserved for the select few patients who are fit for this intensive treatment. Most Canadians with relapsed MCL after BTKi will not be pursuing this therapy. All other available therapies are palliative in nature, and the average survival is <6 months after failure of BTKi therapy. Thus, novel treatments including combinations that are both effective and tolerable are needed to treat the majority of patients with relapsed/refractory disease.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Ibrutinib, a covalent BTK inhibitor, and venetoclax, a BCL2 inhibitor, are small molecules that have different mechanisms of action that are complementary/synergistic when used in combination. Ibrutinib is currently available and funded as monotherapy for relapsed MCL, but venetoclax monotherapy is not an available option for patients with relapsed disease as data is limited. The combination of I+V addresses the underlying disease process and has already been established as an effective regimen in other lymphoproliferative disorders (e.g. CLL). Earlier phase I/II studies for mantle cell lymphoma confirmed high efficacy for this regimen. In the recently published phase III trial comparing ibrutinib + placebo vs. ibrutinib plus venetoclax in patients with relapsed MCL, the I+V combination had a significantly higher progression free survival (33.9 months vs. 22.1 months) compared to ibrutinib, accompanied by higher complete remission rates, confirming the synergistic nature of this combination leading to better outcomes.

The results of this study would be expected to change the current treatment paradigm – since I+V was superior, it would be expected that at time of relapse for any patient that would be treated with BTKi the combination of I+V would be used instead. In most cases, this would be the second line treatment after failure of chemoimmunotherapy with or without HDT-ASCT. This would not impact subsequent eligibility for 3rd line therapies (e.g. CAR T) as patients would have to progress or be intolerant to BTKi before qualifying for CAR T. If the Triangle study is adopted in Canada, in which fixed-duration ibrutinib is used, this would not preclude the use of I+V at relapse if the relapse occurs off therapy – i.e. retreatment with a BTKi would be warranted, and thus I+V would also be reasonable in this setting. Retreatment in this way is already permitted with other fixed duration regimens with these agents (see CDA algorithm for CLL).

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As relapse is expected for patients who have been treated for MCL, these patients will be identified by their treating physicians, usually through clinical examination and diagnostic imaging. Repeat biopsy is not often required, and additional diagnostic tests (other than assessing extent of disease) are not required. Treatment of relapse generally proceeds after relapse has been

confirmed, with very few undergoing an observation period before initiating next line of therapy. Given that BTK inhibitor is the second line treatment for the vast majority of patients, any patient who is eligible to receive ibrutinib for relapsed MCL would be eligible to receive the combination of I+V. The addition of venetoclax requires additional laboratory monitoring and management for mitigating tumor lysis risk, but this monitoring is well established since venetoclax was introduced for CLL nearly 10 years ago. The increase in cardiac risk (mainly arrhythmias and hypertension) is a concern with ibrutinib, and thus cardiac evaluation is recommended as needed before deciding on whether to pursue this combination vs. proceeding with zanubrutinib monotherapy (available only on compassionate access). The I+V combination is effective for all risk groups, thus disease characteristics, stage, etc. would not influence decision to proceed with this regimen.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Patients are assessed regularly while on therapies for relapsed MCL. Clinical assessments are done more frequently in the first 3-6 months to establish that the patient is both tolerating and responding to treatment, and generally includes imaging at various intervals. For ibrutinib monotherapy, the expectation is that the patient achieves a partial response that is sustained while on treatment, with very few achieving a complete response. The I+V combination would have similar expectations, however, more responses including CRs are expected. Once patients are responding and doing well with treatment, long-term follow-up on treatment varies, but generally assessments are every 3-6 months to confirm the patient is still doing well on treatment. Patients should continue to be monitored closely for progression, particularly those who are possible candidates for CAR T therapy, as early relapse detection would permit earlier referral for CAR T treatment and avoid having high burden refractory disease at time of treatment.

The use of oral combinations of novel agents is well established in CLL, and thus similar quality of life, improvement in symptoms, and tolerability of therapies are expected for patients with MCL. These therapies are well tolerated in all patients, but are particularly useful in the older/frailer population where other therapies may not be available or appropriate.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Disease progression and intolerance due to toxicity are the two main reasons to discontinue treatment. In regards to disease progression, this is usually not rapid while the patient remains on treatment, and thus before discontinuation, the next line of therapy is usually determined to avoid a significant flare in disease burden once treatment is discontinued. This is especially important for those patients being considered for CAR T therapy. For intolerance, the toxicities of ibrutinib and venetoclax are quite distinct, and thus depending on which drug is suspected to be causing the toxicity, various approaches can be used. In most cases, dose reductions are initiated first with discontinuation reserved for either severe (life-threatening) or unresolving toxicities. In the case where it is the ibrutinib that is causing toxicity that fails to resolve with dose reduction, the physician may consider replacing this agent with another BTKi (i.e. zanubrutinib), and maintaining its combination with venetoclax which has been used safely and effectively in smaller phase II studies.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

The biggest advantage of this purely oral regimen is that any hematologist that manages patients with MCL can prescribe this combination, in any setting (i.e. community or academic), and does not require any specialized care other than blood work monitoring. As neither drug is new to cancer care, and the combination is already established for CLL, all centres are already trained and equipped to manage patients receiving this treatment.

6. Additional Information

It is clear that the I+V regimen significantly delays progression of this incurable disease. The vast majority of patients will not be candidates for subsequent CAR T therapy (the only effective therapy available for patients who relapse after failure of BTKi), with very poor survival with alternative palliative treatments. By improving PFS earlier in the disease course with I+V combination this will clearly impact long-term outcomes for these patients in a positive way.

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Mona Shafey
Position: Clinical Associate Professor
Date: 12-Feb-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie	X			

AstraZeneca	X			
BeiGene	X			
Kite/Gilead	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Pamela Skrabek
Position: Hematologist, Associate Professor
Date: 21-02-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Hoffmann-La Roche Ltd.	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Carolyn Owen
Position: <Associate Professor University of Calgary and Alberta Provincial Hematology Tumour Group Lead>
Date: 24-02-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche	X			
Abbvie		X		
Beigene		X		

Astrazeneca		X		
Merck	X			
Incyte	X			
Janssen	X			

Declaration for Clinician 4

Name: Dr. Laurie Sehn
Position: Medical Oncologist, BC Cancer
Date: 25-02-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie, Amgen, Astra Zeneca, Beigene, BMS/Celgene, Genmab, Kite/Gilead, Incyte, Janssen, Merck, Seagen, Roche/Genentech	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Kerry Savage
Position: Medical Oncologist, BC Cancer
Date: 28-02-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Seagen	X			

Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.