CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

venetoclax (Venclexta)

(AbbVie Corporation)

Indication: Venclexta (venetoclax), in combination with obinutuzumab, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

June 03, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH 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.

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Patient Group Input: Lymphoma Canada & CLL Canada

Name of Drug: venetoclax

Indication: Venclexta (venetoclax), in combination with obinutuzumab, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

Name of Patient Group: Joint submission by Lymphoma Canada and CLL 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

CLL Canada is a patient driven organization dedicated to enhancing the lives of Canadians affected by Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) through education, advocacy and access to reliable information. www.cllcanada.org

2. Information Gathering

In this submission, we (Lymphoma Canada and CLL Canada) will refer to 2 previous surveys conducted for past CADTH indications involving CLL, one being the original submission for Venetoclax + Obinutuzumab submitted in 2020, and the most recent CLL survey conducted in 2023.

To accurately represent the patient experience and preferences with regard to diagnostics, quality of life, experience with currently available treatments, and expectations in terms of improved outcomes, we will refer to the 2023 anonymous CLL patient survey. This survey was created by Lymphoma Canada and it was promoted by Lymphoma Canada from March 22 to May 2, 2023. 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 was also promoted by CLL Canada to its members as well as on three international CLL patient forums: CLL Support on HealthUnlocked, CLL Archives on acor.org and CLLSLL@groups.io.

The 2023 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. 87 people responded to the survey, 49 identified as Canadians, 12 were from United States, 1 from Australia, and 25 others did not provide

demographic information. The majority of patients were female (52%), diagnosed 9 – 10 years ago (49%), with a variety of chromosome or gene abnormalities, depicted in Tables 1-4.

Table 1: Age range of respondents from 2023 survey

Respondents	Age (years old)					
	45-54	55-64	65-74	75-89	Skipped	Total
Patients with CLL	2	12	26	21	25	62

Table 2: Gender of respondents from 2023 survey

Respondents	Gender			
	Female	Male	Skipped	Total
Patients with CLL	32	30	25	62

Table 3: Number of years ago respondents were diagnosed with CLL (2023 Survey)

Respondents	Years						
	<1	1-2	3-5	5-8	9-10	Skipped	Total
Patients with CLL	4	10	15	8	36	14	74

Table 4: Chromosome or gene mutations of CLL survey respondents (2023 Survey)

Subtype of CLL	Number of respondents
Deletion 17p	8
Deletion 13q	3
Deletion 11q	1
TP53 mutation	2
Trisomy 12	6
Unmutated IGHV	10

Subtype of CLL	Number of respondents
I don't know	45
Skipped	13
Total	74

As mentioned, data was also used from the January 2020 survey which aimed to understand CLL/SLL patients experience WITH venetoclax + Obinutuzumab. This survey was promoted by Lymphoma Canada (LC) and CLL Canada via: email to CLL Canada and the LC database; website posts (cllpag.ca, lymphoma.ca, cllcanada.ca, cllsupport.org.uk); posts on various social media pages and groups; blog posts and online CLL forums. The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into the surveys so respondents were only asked questions relevant to them. Responses from this survey are primarily used to answer section 6 of this submission looking at experience with drug under review.

3. Disease Experience based on the 2023 Survey

At Diagnosis

The development of CLL is very different from other types of lymphomas, in that most patients are diagnosed through routine bloodwork and experience no or minor symptoms at the time of diagnosis. Respondents were asked to rate how much each symptom impacted their quality of life at diagnosis. The highest rated negative impacts (3, 4 or 5, out of 5) amongst 64 respondents were fatigue (47%), high white blood cell counts (leukocytosis) (26%), body aches and pains (25%), enlarged lymph node(s) (23%), and night sweats (20%).

These results are consistent with previous surveys LC and CLL Canada have undertaken for other HTA submissions, including the indication for Zanubrutinib which was submitted to CADTH earlier in 2023.

In terms of psychosocial impacts of CLL diagnosis, the most common factors of 71 respondents were anxiety/worry (61%), stress of diagnosis (59%), and difficulty sleeping (28%).

Current Quality of Life

Survey respondents were asked to rate physical symptoms and psychosocial factors which impacted their current quality of life (70 answered, 17 skipped). The most common negative physical symptoms whose impacts were rated 3, 4 or 5 out of 5, were fatigue (44%), body aches and pains (27%), and indigestion, abdominal pain, or bloating (17%).

CLL had a negative impact on the quality of life of 76% of 87 respondents, the most common impacts being anxiety/worry (42%), difficulty sleeping (31%) and stress of diagnosis (28%).

Daily Activities

Since many CLL & SLL patients do not experience physically debilitating symptoms during the "watch and wait" period before treatment, it is not surprising that many respondents indicated their daily activities were not strongly impacted by their diagnosis. Many respondents indicated their CLL symptoms did not limit their ability to contribute financially to household expenses (80%), however almost half indicated an impact on their ability to spend time with family & friends (45%) or ability to fulfill family obligations (51%).

While the impact of CLL is different from other types of lymphomas, many patients left comments that they still struggle with managing "overwhelming tiredness" and "fatigue which places limitations on daily activities". One patient commented "the stress never really goes away, even after treatment because I am back to watch and wait", while another wrote "the prompt diagnosis and treatment regime helped me to continue living quite normally except for some of the side effects". This highlights the importance and need to continuously manage CLL treatment options in the frontline setting to allow Canadian lymphoma patients to have the best quality of life.

Summary of the Disease Experience

- For many patients, to live with CLL means living with fatigue, anxiety and stress, all of which have a significant impact on a person's quality of life.

4. Experiences With Currently Available Treatments from the 2023 Survey

Due to the nature of CLL, many patients undergo a period of watchful waiting guided by their primary physician or hematologist, before needing to start treatment. It is estimated that 20% to 30% of patients in watch and wait will never require treatment.

Out of 68 patients which provided information on their CLL treatment, 21 indicated they have not received therapy, 26 respondents received one line of treatment, and 19 completed 2 or more treatments. See Tables 5-7 for treatment options provided to CLL patients in first, second and third line of therapy.

Table 5: CLL Treatments in First Line Therapy

CLL treatments	Number of respondents
Ibrutinib	19
Chemoimmunotherapy (FCR and others)	9

CLL treatments	Number of respondents
Ibrutinib + Venetoclax	6
Acalabrutinib	3
Chemotherapy (unspecified)	2
Chlorambucil + Obinutuzumab	2
Venetoclax	1
Rituximab + Bendamustine	1
Acalabrutinib + Venetoclax	1
Total	21

Table 6: CLL Treatments in Second line therapy

CLL treatments	Number of respondents
Ibrutinib	6
Venetoclax	3
Venetoclax + Ibrutinib	2
Acalabrutinib	2
FCR Chemotherapy	2
Rituximab	2
Rituximab + methylprednisolone	1
Zanubrutinib	1
Venetoclax + Rituximab	1
Lenalidomide + Rituximab	1
Total	21

Table 7: CLL Treatments in Third line therapy

CLL treatments	Number of respondents
Venetoclax	3
Ibrutinib	3
Stem cell transplant	1
Chemotherapy + ibrutinib	1

CLL treatments	Number of respondents
Venetoclax + rituximab	1
ABT-199 + Rituximab + Bendamustine	1
Idelalisib + Rituximab	1
Total	11

All CLL patients were asked in the 2023 survey how strongly they agree with the following statement: “My treatment was able to manage my CLL symptoms.” 22% of patients strongly agreed with this sentence, providing a 10 out of 10 rating. The next highest rating was 9 of out 10, which 19% of patients selected.

Overall, less than half of CLL patients are satisfied with the management of their CLL symptoms by the treatment options listed in Tables 5-7.

When asked which side effects were the most difficult to tolerate patients indicated nausea, fatigue, joint pain, skin issues & bleeding, atrial fibrillation, diarrhea, inflammation, bodily aches and pain, headache, muscle weakness, heartburn, indigestion, night sweats, neuropathy, and frequent infections were very challenging during treatment. Furthermore, 26% of patients indicated their CLL treatment had a negative impact on their ability to travel, whereas 19% of patients responded that their treatment had a negative impact on their ability to go to work, school, or volunteer. Here are a few patient quotes collected from LC’s survey to highlight how CLL patients currently feel about their treatment options:

- “I have liked the Venetoclax much more than the Ibrutinib. At the full dose It does increase my tiredness, but I am only going to have to take it for two years so I like that.”
- “I was extremely ill when I started treatment (fatigue, low blood counts, brain fog) so the treatments actually made me slowly feel better. The side effects were probably the symptoms of CLL. Currently the fatigue and brain fog are side effects of the Ibrutinib”
- “My third treatment (venetoclax) relieved my symptoms within a few weeks and there were no side effects.”

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 the majority of survey respondents, including those who believe their current therapy or therapies manage their CLL symptoms well. This indicates a need for alternative CLL treatments with an improved side effect profile.

5. Improved Outcomes from the 2023 Survey

In the 2023 survey, patients were asked about factors important to them when considering a novel CLL treatment. The following factors were rated as extremely important: allow me to live longer (81%), control disease symptoms (75%), bring about a longer remission (71%), better quality of life (66%), and fewer side effects (35%). 56% of respondents indicated it is extremely important (10 out of 10) to have choice in their treatment decision, while 55% reported it is very important to have increased treatment options available to choose from.

This was echoed by several patients who indicated they would like choice when it comes to the therapy they receive:

- "I would like to have a choice of medications rather than just the 420 mg of daily Ibrutinib I have been on the past 3 years. It was the only option given to me."
- "More options for combination therapies at start of treatment"

CLL patients were asked in the 2023 survey whether they would prefer to take a novel therapy over fixed duration vs. novel therapy required to be taken indefinitely. 24% of patients reported preferring the fixed duration treatment versus 10% continuous therapy, and 66% reported they were not sure.

These results reflect the fact that the choice of treatment is rarely a simple, straightforward decision. Rather, multiple dimensions need to be considered, including the time and cost required to travel to a hospital as well as the constraints posed by family, caregiving and work responsibilities. Having a preference for a fixed duration therapy aligns with this submission, as Ven + Obin is being requested to be funded as a fixed duration targeted therapy for the fit population.

The answers to this question further underline the importance of giving patients treatment options that they can discuss with their doctors and their loved ones. They can then make their treatment decision

considering all the relevant factors, both medical (effectiveness, side effects, comorbidities, etc.) as well as the constraints and issues related to their life circumstances.

This is reflected by several patients which commented on what they want in novel CLL treatments:

- "If available my preferred treatment would be a time-limited or fixed duration oral therapy without or minimal side effects. Ideally a treatment which is curative."
- "I am hopeful that a new drug therapy will be found to cure CLL so that patients once treated will be cured and no longer have to face repeated treatment therapies for the rest of their lives."
- "My expectations would be that a new drug therapy would offer symptom relief, would increase the quality of life, a longer life expectancy with quality of life."

Summary of Improved Outcomes

- CLL patients identified factors important for novel treatments, which included longer life span, longer remission, better quality of life and fewer side effects.
- A large 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

Information in this section was compiled from the survey of CLL/SLL patients WITH frontline Venetoclax and Obinutuzumab experience done in 2020 for the Lymphoma Canada/CLL Canada joint submission on Venetoclax and Obinutuzumab (ven+obin).

A total of 33 patients reported experience with ven + obin. 10 of these patients were aged 40-59 years old, and 22 patients being between 60-79.

Respondents	CAN	USA	UK	AUS	Skipped	Total
CLL/SLL patients WITH ven + obin experience	2	29	1	0	1	33

Respondents	Age					Gender		
	21-39	40-59	60-79	80-89	N/A	M	F	N/A
CLL/SLL patients WITH ven + obin experience.	0	10	22	0	1	18	14	1

Patients were asked if they were able to complete the full course of treatment with Venetoclax and Obinutuzumab. All patients are still receiving venetoclax or completed treatment; only 2 patients were not able to complete the full course of obinutuzumab infusions, due to side effects:

Completed treatment?	Venetoclax (N = 33)	Obinutuzumab (N = 33)
Yes	9 (27%)	18 (55%)
Still receiving treatment	24 (73%)	13 (39%)
No, due to side effects	0 (0%)	2 (6%)
No, because CLL/SLL progressed	0 (0%)	0 (0%)

Additionally, patients were asked if any of their CLL symptoms were not managed by ven + obin. Over half of patients (20/33; 61%) reported that treatment managed all their symptoms. Symptoms that were not managed by treatment in more than 10% of respondents included fatigue/lack of energy (10/33; 30%), and shortness of breath (4/33; 12%).

Overall, most individuals (31/33; 90%) noted that they had a positive experience with ven + obin (rating = Good, Very good, or Excellent) and 85% of patients noted their experience with treatment was “very good” or “excellent”.

When asked about the impact of treatment-related side effects on quality of life, most respondents noted that treatment side effects had “no” or “some” impact on their quality of life. Fewer than 1/5 of respondents (15-18%) noted that treatment side effects had a “significant” or “very significant” impact on their quality of life. This is significant because as noted from the 2023 survey, CLL patients had indicated how current therapies continue to have a negative impact on their quality of life (76%). Hence therapies like Ven + Obin are needed as it aligns with the patient preference for improved quality of life.

These responses further coincide with data collected from the CLL13 study, as patients who received Ven+O experienced fewer side effects and were therefore less likely to discontinue treatment early. At the 4 year analysis, 18.5% and 6.1% of patients in the CIT and VenO arms, respectively, had discontinued treatment early. Of this, 14.8% and 3.9% were due to adverse effects. As patients in our surveys indicated that decreased toxicity is very important to them in terms of new treatments, CLL patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a range of patients.

Below are some comments once again from the original submission from patients with experience with this therapy:

- *I have my life back better than expected by a high degree of measure.*
- *For me this treatment was efficacious, tolerable, expedient, and appealing because it allowed the possibility for discontinuation as compared to the BTK's. I discontinued treatment December 12, 2019. I am very satisfied with the immediate response from obinutuzumab plus venclexta, and I hope to experience a reasonable durability of at least five years.*
- *I am on a maintenance dose of Venetoclax now. As time goes on after the 1 year mark, I'm*

getting much stronger.

- *Essentially no side effects for me. Very easy ride so far and my CBC numbers are looking very good.*

7. Companion Diagnostic Test

N/A

8. Anything Else?

Many CLL patients need different treatments over time as their disease progresses. Because patients respond differently to treatments, it's important to have a variety of options that are easy to manage. Notably, 35% of patients said that having fewer side effects is their top priority, showing a strong preference for treatments that minimize side effects. As a result of the harsh side effects, it is no surprise that patients are showing preference for time limited novel therapies over chemotherapy. Venetoclax + obinutuzumab provides an effective frontline option with limited treatment duration that has mild side effects for most, which will permit patients to maintain or regain a good quality of life, have fewer hospital visits and contribute to society. Hence, it is important that the reimbursement criteria for Ven+O to be expanded, making sure that now ALL previously untreated patients with CLL can have the option of Ven+O in the firstline setting.

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.

   Lymphoma Canada & CLL Canada collaborated to complete this submission.

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 – Lymphoma Canada

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
Janssen				X
AstraZeneca				X
BeiGene				X
AbbVie				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 & Advocacy

Patient Group: Lymphoma Canada

Date: June 3, 2024

Table 2: Financial Disclosures – CLL Canada

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
Janssen	X			
AstraZeneca	X			
BeiGene			X	
AbbVie	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: Raymond Vles

Position: Board Chair

Patient Group: CLL

Canada **Date**: June 3 2024

Clinician Group Input: Ontario Health (Cancer Care Ontario)

CADTH Project Number: PC0362

Generic Drug Name (Brand Name): venetoclax (Venclexta)

Indication: Venetoclax, in combination with obinutuzumab for the subgroup of previously untreated CLL patients considered potentially fludarabine-eligible, who were not included in the reimbursement request or recommendation criteria in the previous CADTH review (PC0212-000). Note that based on this request, the reimbursement criteria for venetoclax in combination with obinutuzumab would be expanded for the previously untreated CLL patients, irrespective of age or eligibility for fludarabine treatment (i.e., aligned with the Health Canada indication).

Name of Clinician Group: Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Author of Submission: Dr. Tom Kouroukis

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 by email.

3. Current Treatments and Treatment Goals

This treatment would be considered for first line therapy for CLL. Currently, the standard of care would include venetoclax + obinutuzumab (for high-risk cytogenetics), obinutuzumab + chlorambucil, bendamustine, and FCR. Also, a BTK inhibitor would be used for patients with high risk genetics (i.e. 17p deletion, TP53, unmutated IGHV).

Figure 1: Provisional Funding Algorithm Diagram for Chronic Lymphocytic Leukemia (General Population Without High-Risk Cytogenetic Markers)

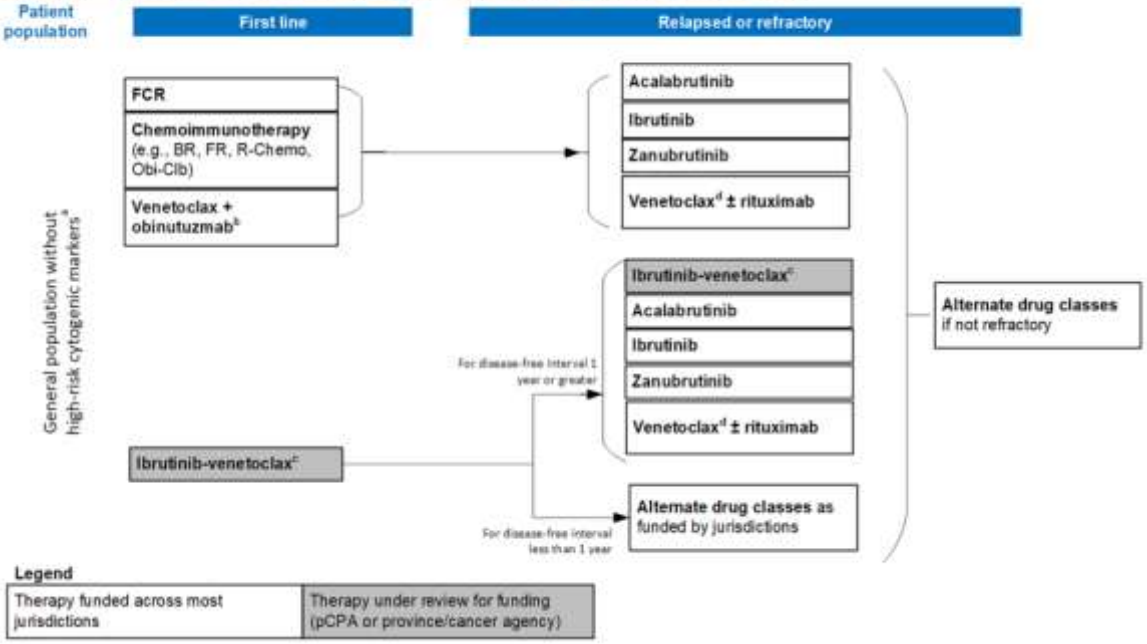
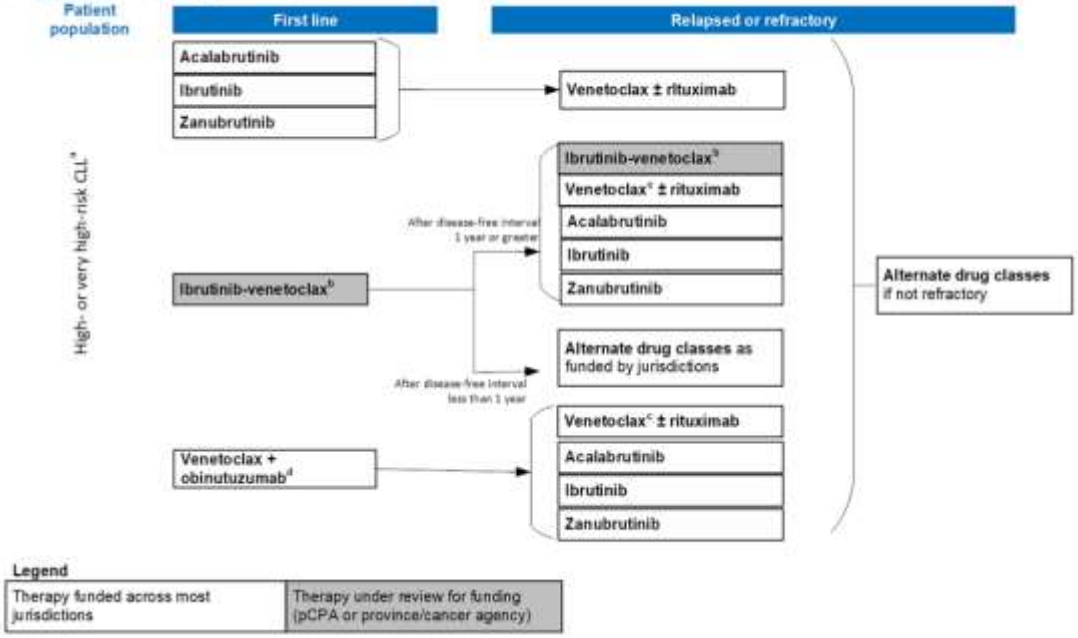


Figure 2: Provisional Funding Algorithm Diagram for Chronic Lymphocytic Leukemia (High or Very High Risk)



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.

This is an immunotherapy option that is not combined with chemotherapy.

5. Place in Therapy

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

This would be used as first line in all patients with CLL requiring therapy.

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?

All patients with CLL requiring therapy who would be able to receive intravenous obinutuzumab.

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 CLL response outcomes, improvement in progression free survival, reduction in symptoms and improvement in quality of life.

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

This is a fixed duration therapy. Earlier discontinuation will be based on significant intolerance 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]?

Any systemic therapy center by prescribers familiar with the treatment of CLL. Additional lab monitoring may be required during venetoclax ramp-up.

6. Additional Information

N/A

Appendix: Ontario Health (Cancer Care Ontario) 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) provided a 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 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. Tom Kouroukis

Position: Lead OH (CCO) Hematology Cancer Drug Advisory Committee

Date: 18-04-2024

☒ **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

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				

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

Clinician Group Input: Lymphoma Canada

CADTH Project Number: **PC0362-000**

Generic Drug Name (Brand Name): venetoclax (venclexta)

Indication: previously untreated CLL (in combination with Obinutuzumab)

Name of Clinician Group: Lymphoma Canada – Canadian hematologists

Author of Submission: Carolyn Owen, Abi Vijenthira, Lin Yang, Alina Gerrie, Nathalie Johnson, Nicole Laferriere

1. About Your Clinician Group

Lymphoma Canada is a patient advocacy group that helped organize hematologists to complete this requested feedback letter.

2. Information Gathering

Group consensus of Canadian hematologists (via email).

3. Current Treatments and Treatment Goals

The firstline treatment of CLL has seen significant change in the last 10 years with the entry of oral, targeted therapies into the treatment landscape. All studies of targeted therapy compared against chemotherapy/chemoimmunotherapy have demonstrated an advantage of targeted therapies (in terms of progression-free survival (PFS) and sometimes also overall survival (OS)). Based on these many studies, targeted therapies are generally now the standard of care for firstline therapy in CLL with options for treatment varying between provinces but including venetoclax and obinuzumab for 12 months fixed duration, ibrutinib and venetoclax for 12 cycles of combination therapy and indefinite BTKi monotherapy (ibrutinib, acalabrutinib or zanubrutinib). As indefinite BTKi therapy is associated with a larger cost/budget impact, this choice is restricted to patients with higher risk genomic features in some provinces but is not restricted by age/fitness. Some provinces do not restrict access to BTKi and in those provinces, the proportion of patients treated with BTKi has been increasing over the last several years. Venetoclax and Obinutuzumab (like the other targeted therapies) was first examined in patients with comorbidities and was thus, funded only in that population. Since that original publication, the German CLL Study Group has completed a study specifically in younger, fit patients and confirmed the efficacy and tolerability of Ven+O in those patients. The current request is to fund Ven+O as a fixed duration targeted therapy in these younger and fit patients such that now **all** previously untreated patients with CLL would have the option of Ven+O as firstline treatment. This funding approach would be expected to save money as Ven+O would replace indefinite BTKi for many patients. Although chemoimmunotherapy with FCR is also an option for good risk, young and fit patients, this therapy is infrequently used in Canada and is associated with a 6% risk of therapy-associated myeloid neoplasms, a disease with high risk of mortality that young patients typically wish to avoid. The use of Ven+O (particularly in ALL good-risk patients with CLL) is the recommended approach in a consensus guideline by Canadian hematologists (see Owen C et al, Leukemia Research 2022 publication). There are several reasons to favour Ven+O

as a firstline treatment approach including: better cost compared to BTKi monotherapy approach, access to anti-CD20 monoclonal antibody, obinutuzumab is ONLY accessible to patients with CLL in the firstline setting so this effective therapeutic agent would be lost if Ven+O was not selected; Ven+O is very well tolerated with increasing Canadian experience and comfort with the regimen, Ven+O choice over Ibr+ven would allow the avoidance of BTKi which theoretically could reduce the chance of resistance to BTKi via clonal selection in the relapsed setting (no data currently exists to determine if Ven+O is better/worse or equivalent to IBR+Ven which CADTH has recommended broadly for all patients with CLL in the frontline but some experts favour Ven+O for this theoretical reason while longer term data is obtained); Ven+O avoids cardiac risks of IBR+Ven combination regimens (where cardiac risks including fatal cardiac events were seen in both younger and older patient populations).

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.

Currently, the only way to obtain Ven+O for a younger patient with higher risk genomic features (like unmutated IGHV) is to argue that the poor-risk genomic feature meets the definition of fludarabine-inappropriate/ineligible. While it is true that fludarabine/chemotherapy is ineffective in this population, the definition of fludarabine-ineligible in the clinical trials was not based on the CLL-disease characteristics but on the patient age/comorbidities. The current requested change in funding/wording clarifies that these patients should have access to Ven+O to ensures fairness and equitable access across the country and to reduce confusion. Additionally, the expanded funding will allow the youngest/fittest patients with good-risk disease and the longest life expectancy to benefit from highly-effective targeted therapy and avoidance of FCR with its associated risk of short and long-term bone marrow toxicities including febrile neutropenia/pancytopenia and secondary myeloid malignancy.

5. Place in Therapy

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

The requested change in funding wording would be in keeping with CADTH's current provisional funding algorithm for CLL. The option of Ven+O frontline for all patients should encourage deferring indefinite BTKi-based therapy to the relapsed/refractory setting for the majority of patients, which is expected to reduce the budget impact of CLL therapy and would be in keeping with patient preferences of accessing fixed duration targeted therapy frontline.

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?

All patients with CLL who require firstline therapy would benefit from this therapy. Currently, many already have access based on current provincial funding. All patients with CLL would benefit from frontline targeted therapy that is fixed duration. The only patients for whom this therapy might be inferior are those with del(17p)/TP53mutation in whom the outcomes of Ven+O are inferior to those without these high risk genomic features. Such patients typically receive BTKi monotherapy and are unlikely to be offered Ven+O or IBR+Ven however; these fixed duration

therapies are still significantly better than chemo/chemoimmunotherapy and should be available for the rare patient who is strongly desiring of fixed duration therapy.

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?

Lack of response to Ven+O is exceptionally uncommon. Response assessments in CLL in routine practice are performed clinically by physical exam and review of blood work and this would not be changed/influenced by this expanded access to Ven+O

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

<Therapy would be discontinued if a lack of response (extremely unlikely) or abbreviated in the setting of significant toxicity (but clinical benefit may still be obtained if the therapy was abbreviated).>

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]?

Any specialist physician who treats CLL should be able to provide/supervise therapy with Ven+O. This expanded access will now include patients who are younger/fitter than those who already have access to Ven+O so these patients are expected to tolerate therapy better and have less difficulties with the necessary blood work/visits.

6. Additional Information

<N/A>

Appendix: Lymphoma Canada 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. Only help from Lymphoma Canada to circulate the responses and obtain feedback/edits from other hematologists.

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.**

1.1 Declaration for Clinician 1

Name: Carolyn Owen

Position: Associate Professor, University of Calgary

Date: 30-04-2024

☒ **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.

1.1.1 Table 1: Conflict of Interest Declaration for Clinician 1

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		
Astrazeneca			X	
Beigene			X	

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

1.2 Declaration for Clinician 2

Name: Abi Vijenthira

Position: Hematologist, Princess Margaret Cancer Centre

Date: 05-05-2024

☒ 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.

1.2.1 Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

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

1.3 Declaration for Clinician 3

Name: Lin Yang

Position: Hematologist, University of Manitoba

Date: 05-06-2024

☒ 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.

1.3.1 Table 2: Conflict of Interest Declaration for Clinician 3

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	
Beigene	X			
Lilly	X			

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

1.4 Declaration for Clinician 4

Name: Nathalie Johnson

Position: Hematologist Jewish General Hospital Date: 04-05-2024

☒ 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.

1.4.1 Table 2: Conflict of Interest Declaration for Clinician 4

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	
Roche			x	
Beigene		x		
Astra Zeneca		X		
Janssen		x		

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

1.5 Declaration for Clinician 5

Name: Alina Gerrie

Position: Hematologist, BC Cancer; Assistant Professor, University of British Columbia> Date: <30-04-2024

☒ 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.

1.5.1 Table 2: 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
Astrazeneca		X		
Beigene	X			
AbbVie		X		
Celgene	X			
Lilly	X			

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

1.6 Declaration for Clinician 6

Name: Nicole Laferriere

Position: Hematologist, Thunder Bay Regional Health Sciences Centre

Date: 30-04-2024

☒ 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.

1.6.1 Table 2: 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
Astrazeneca		X		
Beigene	X			
AbbVie		X		

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