CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

venetoclax (Venclexta)

AbbVie Corporation

Indication: In combination with azacitidine for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

July 22, 2021

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0238-000
Brand name (generic)	Venclexta (venetoclax)
Indication(s)	Acute Myeloid Leukemia
Organization	Canadian Leukemia Study Group (CLSG/CGEL)
Contact information[a]	Name: Joseph Brandwein Email: [redacted] Phone: [redacted]

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

While we are generally pleased with your recommendation to reimburse with conditions, the members of the CLSG executive would like to bring to your attention a number of inaccuracies regarding the cost-effectiveness analysis, which we feel should be taken into consideration:

1. Azacitidine cost: The cost quoted ($8,400 per cycle or $100,800 for 12 cycles) is for the brand name Vidaza. Most centres in Canada are now using generic azacitidine from Reddy's Laboratories, and have negotiated a cost of approximately $240 per 100 mg vial. The actual cost is therefore $3,360 per cycle, or $40,320 for 12 cycles.

2. The costing of venetoclax is based on continuous dosing at 400 mg daily through the entire 28 day cycle. In the Viale A study, approximately 70% of patients had at least a one week reduction in treatment duration (i.e. to 21 days per cycle) after achieving complete remission, due to neutropenia +/- thrombocytopenia. Some of these (20-30%) had a subsequent reduction to 14 days per 28 day cycle, again mainly due to neutropenia. That is also the experience of physicians in Canada who have used this combination. Therefore, the average price calculation after achieving CR (generally from cycle 2 onward) should be reduced by 25% to account for this reduced average treatment duration.

3. Most physicians using the aza/venetoclax combination also use anti-fungal prophylaxis, usually with an azole drug (either fluconazole, posaconazole or voriconazole). This is done to reduce the risk of neutropenia-related fungal infections (according to ASCO/IDSA Clinical Practice Guidelines for neutropenia $\geq$ 7 days), and to reduce the cost of the venetoclax. Amongst Canadian leukemia physicians who have used the aza/ven combination, the use of azole antifungals is almost universal.

   Due to CYP3A4 drug interactions, the concomitant use of azoles requires a dose reduction in venetoclax. For strong CYP3A inhibitors such as posaconazole this requires at least an 80% venetoclax dose reduction (to 50-70 mg per day), while the use of a moderate inhibitor such as fluconazole requires a 50% dose reduction in venetoclax (to 200 mg daily) to achieve comparable serum levels.

   The price quoted for venetoclax is $70 per 100 mg tablet = $280 per day, or $7,840 per cycle ($94,080 per 12 cycles). Given the considerations outlined in 2 and 3 above, the actual average cost of venetoclax, if used in conjunction with fluconazole, would be $3,920 for cycle 1 (28 days) and $2,940

for cycles 2 – 12 (21 days). Therefore, the total cost for 12 cycles of venetoclax would be $36,260. If posaconazole is used, this cost would be considerably less, but this agent is much more expensive than fluconazole.

Although not a cancer drug, the cost of the antifungal agent would also need to be taken int o consideration. The cost of generic fluconazole would be approximately $8,000 per year.

Therefore, the estimated total cost of this combination treatment per year would be as follows:

Cycle 1: azacitidine $3,360 + venetoclax $3,920 = $7,280
Cycle 2-12: azacitidine $3,360 + venetoclax $2,940 = $6,300 per cycle, or $69,300
Fluconazole = $8,000 (approx.) for 12 cycles
Total cost for one year = $7,280 + $69,300 + $8,000 = $84,580.

This total is considerably less that that used in the analysis, and would be more reflective of the expected real-world use of this combination in Canada. We would therefore respectfully recommend that your analysis be recalculated to take these numbers into consideration.

We would also advocate using azacitidine as the comparator for this analysis, is it is the most widely used single agent for this indication in the country, accounting for around 70% of patients who receive non-intensive single agent therapy (vs. approximately 30% for low-dose cytarabine). Furthermore, most of those who receive low-dose cytarabine (patients who progressed on azacitidine for MDS or who live too far from a cancer centre to receive azacitidine) would not be eligible for venetoclax + aza, for the same reasons.

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

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

[a] CADTH may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by CADTH.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 – Joseph Brandwein • Clinician 2 – Andre Schuh • Clinician 3 – Brian Leber • Clinician 4 – Julie Bergeron • Clinician 5 – Lalit Saini • Clinician 6 – Mary Lynn Savoie • Clinician 7 – Waleed Sabry • Clinician 8 – Kristjan Paulson • Clinician 9 – Yasser Abou Mourad • Clinician 10 – John Storring		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*

Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3

Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
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Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0238-000
Brand name (generic)	Venclexta (venetoclax) Manufacturer: AbbVie
Indication(s)	**Indications:** Venclexta is indicated, in combination with a hypomethylating agent or in combination with low-dose cytarabine, in adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy. **Manufacturer Requested Reimbursement Criteria[1]:** In combination with azacitidine for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Organization	Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (Hem DAC)
Contact information[a]	Name: Dr. Tom Kouroukis Email: [redacted] Phone:

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification. Question arised based on the economic analysis – the cost of azacitidine is much lower with generics than stated in the report.		

It is unclear why the reported pharmaeconomic ICER comparator was LDAC instead of azacitidine from the VIALE-A trial. It would be relevant to know the ICER compared to azacitidine, given azacitidine is the current standard of care. There are cost mitigation strategies of using CYP3A inhibitors to lower venetoclax dosing and these were not discussed.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

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  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it. OH-CCO provided secretariat support to the DAC in completing this feedback.		
2. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Tom Kouroukis • Dr. Pierre Villeneuve • Dr. Lee Mozessohn • Dr. Jordan Herst • Dr. Janet MacEachern (DAC term completed in March 2021) • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

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New or Updated Declaration for Clinician 2	
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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

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Add or remove rows as required	☐	☐	☐	☐

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Date	*Please add the date form was completed (DD-MM-YYYY)*
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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0238
Name of the drug and Indication(s)	Venetoclax with azacitidine for AML
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	x
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
None.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
In the Background section, PAG is suggesting the following revision, *"Dose adjustments of venetoclax are required for patients receiving medications that are strong and moderate inhibitors of CYP3A enzymes."* In the Economic Evidence section, cost per course, PAG is requesting an updated price reduction of venetoclax using the publicly available list price.
b) Reimbursement conditions and related reasons
None.

c) Implementation guidance
In the Implementation Guidance section, sixth bullet, PAG is suggesting the following revision "Clinical experts indicated that, in clinical practice, azacitidine is *also* administered on a 5-2-2 dosing schedule." In the Implementation Guidance section, seventh bullet, PAG is suggesting the following revision "There is no evidence to inform on the appropriate time frame to consider adding venetoclax to the treatment regimen of patients who are currently *also* receiving single agent azacitidine." In the Implementation Guidance section, PAG is seeking clarity on whether high-risk MDS patients who aren't fit for intensive induction chemotherapy could use venetoclax and azacitidine as part of upfront treatment. In the Discussion Points section, seventh bullet, PAG agrees that this text belongs in the Implementation Guidance section. In the Discussion Points section, eight bullet, PAG agrees that the following, "Based on these data, it would be reasonable to consider the use of venetoclax plus azacitidine in patients with a history of treatment with a HMA for MDS" belongs in the Implementation Guidance section. In the Discussion Points section, ninth bullet, PAG agrees that the following, "Therefore, pERC suggested that venetoclax plus azacitidine could be considered as a treatment option in patients with TP53 mutations" belongs in the Implementation Guidance section. In the Discussion Points section, eleventh bullet, PAG is suggesting the following revision, "Feedback from clinical experts suggested that age is not a necessary component of eligibility *for induction chemotherapy*."