CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

ivosidenib (Tibsovo)

(Servier Canada Inc.)

Indication: TIBSOVO (ivosidenib) in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.

July 03, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0349-000
Brand name (generic)	Tibsovo (ivosidenib)
Indication(s)	Acute myeloid leukemia (AML)
Organization	The Leukemia & Lymphoma Society of Canada (LLSC) ***Amended submission**
Contact information[a]	Name: Colleen McMillan [redacted]

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

We agree that ivosidenib + azacitidine addresses several of the unmet needs identified by patients, as it improves disease control and prolongs survival. Additionally, it provides a much-needed treatment option for this patient population, particularly given the limited therapies available for those with newly diagnosed AML who have an IDH1 mutation and are ineligible for standard intensive chemotherapy.

We understand CDA's comment about lack of head-to-head study against the current standard of care but want to emphasize that the current standard of care is a newer treatment that was not available at the time that ivosidenib was in trials. We also want to emphasize that molecular targeted therapy is a standard of care, and it is recognized that therapy that is able to target a molecular driver of cancer is accepted to be preferable to one that is not. While the trials that are used to demonstrate efficacy of ivosidenib in the IDH1 population are not the standard randomized trials, we disagree that the trial design limited CDA's ability to draw conclusions of efficacy. Targeted therapies by nature, treat smaller populations which make it difficult to conduct large trials.

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

We appreciate the committee's recommendation and recognition that transfusion independence and infection rates are important endpoints for both patient groups and clinicians, as they can significantly affect patients' quality of life. The acknowledgment that ivosidenib + azacitidine may reduce the need for transfusions, potentially leading to fewer infections compared to placebo + azacitidine, is particularly valuable

We did, however, identify a clerical error in the report. In the Clinician input section, LLSC's Clinician Network was referred to only as "LLSC". To clearly distinguish between the input from LLSC's patient group and the LLSC Clinician Network's input, please refer to the clinician group as "LLSC Clinician Network"

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

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Colleen McMillan*
Position	*Advocacy Lead, LLSC*
Date	*19-09-2024*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

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

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☒
	Yes	☐

D. New or Updated Conflict of Interest Declaration

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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Servier	☐	☒	☐	☐
AbbVie	☐	☐	☐	☒

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0349-000
Brand name (generic)	Tibsovo (ivosidenib)
Indication(s)	in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.
Organization	OH (CCO) Hematology Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Tom Kouroukis

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

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

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

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

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. 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?	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		

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0349
Name of the drug and Indication(s)	Ivosidenib
Organization Providing Feedback	PAG

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

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. Please ensure that IDH1 R132 is explicitly specified every time the mutation is mentioned.

Version: 1.0
Publication Date: TBC
Report Length: 2 Pages

c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0349
Brand name (generic)	TIBSOVO® (ivosidenib)
Indication(s)	In combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.
Organization	Servier Canada Inc. (Servier)
Contact information[a]	[redacted]

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

Servier agrees with the committee's recommendation that TIBSOVO + azacitidine be reimbursed for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive intensive induction chemotherapy, in line with the reimbursement conditions outlined in Table 1 of the recommendation document.

AML is a life-threatening condition, and the majority of patients are elderly. Moreover, IDH1-mutated AML is considered a rare condition, representing only 6-10% of all AML cases. Some patients with newly diagnosed AML are ineligible for standard intensive chemotherapy because of their advanced age, as well as poor performance/functional status and/or a comorbid medical condition (estimated to be 40-50% of all AML patients); this further limits the population of interest for this review. Approved and reimbursed treatment options in Canada for AML patients who are not considered suitable for intensive induction chemotherapy are limited and include single-agent low-intensity chemotherapy [azacitidine, low-dose cytarabine (LDAC)] or VENCLEXTA® (venetoclax) + azacitidine. There is currently no access to IDH1-targeted treatment options. Given this context, Servier is pleased to see that the committee deliberated on TIBSOVO considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CDA-AMC Reimbursement Reviews.

Overall, TIBSOVO + azacitidine represents a new option within the complex and multifactorial treatment landscape for AML patients ineligible for standard intensive chemotherapy. TIBSOVO + azacitidine is the first and only IDH1 mutation-targeted therapy to have demonstrated significant clinical and patient benefit in a robust randomized controlled trial designed specifically for the IDH1-mutated population. Notably, TIBSOVO + azacitidine demonstrated a significant improvement in overall survival (OS) compared to placebo + azacitidine; as per the last available data cutoff (DCO), median OS was 29.3 months [95% confidence interval (CI), 13.2-not estimable (NE) months] in the TIBSOVO + azacitidine arm and 7.9 months (95% CI, 4.1-11.3 months) in the placebo + azacitidine arm [hazard ratio (HR) = 0.42; 95% CI, 0.27-0.65; p = <0.0001].

By contrast, VENCLEXTA is not an IDH1-targeted agent; rather, it is a small molecule inhibitor of B-cell lymphoma 2 (BCL-2), a protein that inhibits cells from programmed cell death. In the population

of interest (IDH1-mutated AML patients not eligible to intensive induction chemotherapy), evidence for VENCLEXTA + azacitidine is limited to exploratory *post hoc* subgroup analyses in a small sample size of 34 patients. To this point, Servier would like to request an editorial change on page 10 of the recommendation, where it is noted that *"In the VIALE-A study (venetoclax + azacitidine vs. placebo + azacitidine), approximately 25% of patients harbored an IDH1 or IDH2 mutation."* Of relevance to this review is the reporting of the proportion of patients with only an IDH1 mutation, which is ~8% (34/431) of patients in VIALE-A.

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	☒

While Servier agrees with the recommendation as a whole, and is not requesting any further revisions, Servier would like to highlight three key points of feedback that were provided on the pharmacoeconomic review report (PRR). These points are reiterated below.

The first point is related to CDA-AMC's comments on the insufficiency of the available clinical evidence to justify a price premium. There are multiple potential benefits of TIBSOVO + azacitidine over VENCLEXTA + azacitidine, which were neglected. The submitted evidence, as well as input from practicing AML-treating clinicians, suggest the following benefits in favour of TIBSOVO + azacitidine, which should be considered when assessing the overall value of the treatment:

- Lower risk of myelosuppression and infections, as well as lower rates of hospitalization for adverse events (AEs) that are recognized by clinicians to result in hospitalization. Indeed, both clinician groups that provided input on this review suggested that treatment with VENCLEXTA + azacitidine is associated with increased risk of neutropenic fever and infections compared to azacitidine alone. According to the clinicians, infections may result in hospitalizations, which in many cases can be days to weeks depending on severity.
- Ease of use, with no dosage ramp-up and monitoring at initiation for tumor lysis syndrome (TLS) (and thus less resource utilization at initiation). Clinician input from LLSC suggested that no TLS monitoring is required with TIBSOVO + azacitidine.
- Median OS of 29.3 months, which is almost two-to-three times that observed for VENCLEXTA + azacitidine in VIALE-A (14.7 months in the ITT population; 10.2 months in the IDH1-mutated subgroup)

The improved efficacy and tolerability demonstrated by the totality of clinical evidence, as well as the favourable stakeholder input, contradict the conclusion that there is insufficient clinical evidence to justify a price premium.

The second point is related to the CDA-AMC reanalysis of survival extrapolation using the exponential model. This model does not represent the expected pattern of survival for this patient population i.e., an initial drop in the survival curve, followed by a levelling out, and then (in the long-term) an increase in mortality risk in line with age. The original choice of the log normal extrapolation for both event-free survival (EFS) and OS, as submitted by Servier, was based on visual inspection of fit of the observed curves and the statistical fit of the curve parameters from the AGILE trial. The calculated Akaike information criterion (AIC) for log normal was the lowest amongst the other parametric fits, suggesting a best statistical fit for TIBSOVO + azacitidine for both EFS and OS. The clinical plausibility of this extrapolation was validated by clinical experts consulted by Servier. Furthermore, data from the VIALE-A study also indicated that the estimated OS rate at 24 months was 37.5% for VENCLEXTA + azacitidine, which is aligned with the extrapolated OS rate for TIBSOVO + azacitidine at 24 months (38.7%). A log normal selection for both EFS and OS results in

an incremental cost effectiveness ratio (ICER) value of approximately $500,000/QALY when compared with VENCLEXTA + azacitidine.

The third point is related to the cure state assumption in the analysis. CDA-AMC assumed that AML patients experience cure after 10 years, which may not be appropriate. Clinical experts consulted by Servier concluded that during the 5th year, it is shown within their clinical practice that patients who remained in the EFS health state (with CR/CRi) have a significantly reduced risk of experiencing relapse. Furthermore, based on the visual inspection of fit to the Kaplan Meier (KM) plots, the EFS KM curve plateaus at the end of the 24th and the 23rd months for TIBSOVO + azacitidine and VENCLEXTA + azacitidine, respectively. A 60-month cure state assumption was deemed conservative, and the expected risk of progression is considered low. Servier's approach is aligned with a peer reviewed Canadian publication.[1] As well, the recent NICE Technology Appraisal guidance for TIBSOVO + azacitidine described a 3-year cure assumption as reasonable and plausible based on the plateau of the KM curve as 41% of people on TIBSOVO + azacitidine were estimated to be still alive at 3 years.[2] Using a 5-year cure state in the CDA-AMC base case reduces the ICER to approximately $800,000/QALY compared with VENCLEXTA + azacitidine.

When a 5-year cure state is combined with a log-normal distribution for both EFS and OS, the ICER further decreases to approximately $406,000/QALY; this is $800/QALY lower than the CDA-AMC re-analysis of $1,206,919/QALY.

References:

1) Guinan K, Mathurin K, Au Y, et al. Venetoclax in Combination with Azacitidine for the Treatment of Newly Diagnosed Acute Myeloid Leukemia: A Canadian Cost-Utility Analysis. Curr Oncol. 2022 Oct 8;29(10):7524-7536.
2) NICE. Technology appraisal guidance – TA979. Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation. Published: 05 June 2024. (https://www.nice.org.uk/guidance/ta979/documents/html-content-5)

Clarity of the draft recommendation

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

N/A

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

Servier would like to highlight that there is inconsistency in the reporting of IDH1 mutation testing use/availability throughout the recommendation. On page 5, under *Feasibility of adoption*, the following is stated: *"Clinical experts indicated that IDH1 mutation testing is not part of routine AML diagnostic testing for all jurisdictions across Canada…"* This is re-iterated at the bottom of page 5. However, on page. 10 under *Care provision issues*, the following is stated: *"The clinical experts noted that most, but not all, leukemia-treating centres have routine access to PCR testing for IDH1 mutation."*

Servier would like to note that in its discussions with clinical experts, it was indicated that, in Canada, IDH mutation testing is available and already a part of routine diagnostic practice for AML patients.

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

N/A

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