CADTH

CADTH REIMBURSEMENT REVIEW

Pharmacoeconomic Report

Decitabine and cedazuridine (INQOVI)

Taiho Pharma Canada, Inc.

Indication: The treatment of adult patients with MDS including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk IPSS groups.

Version: Final
Publication Date: September 2021
Report Length: 17 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AAMAC Aplastic Anemia and Myelodysplasia Association of Canada

AML acute myeloid leukemia

CMML chronic myelomonocytic leukemia

HSCT hematopoietic stem cell transplant

ICER incremental cost-effectiveness ratio

INT-1 intermediate-1

INT-2 intermediate-2

IPSS International Prognostic Scoring System

NMA network meta-analysis

NOC notice of compliance

MDS myelodysplastic syndromes

mg milligram

OS overall survival

QALY quality-adjusted life year

Executive Summary

The executive summary comprises two tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Decitabine/cedazuridine (Inqovi), 35 mg decitabine / 100 mg cedazuridine tablets
Submitted price	Decitabine/cedazuridine, 35 mg / 100 mg: $879.20 per tablet
Indication	For the treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.
Health Canada approval status	NOC
Health Canada review pathway	Other – Project Orbis
NOC date	July 7, 2020
Reimbursement request	As per indication
Sponsor	Taiho Pharma Canada, Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance; MDS = myelodysplastic syndromes; mg = milligram.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with de novo or secondary myelodysplastic syndrome (MDS) who are not considered candidates for hematopoietic stem cell transplantation. The base case population was split into three subgroups: • Intermediate 2 to high-risk MDS (INT-2 to high-risk MDS) • Intermediate 1 MDS (INT-1 MDS) • chronic myelomonocytic leukemia (CMML)
Treatment	Decitabine/cedazuridine[a] in addition to BSC (consisting of red blood cell and platelet transfusions, antibiotics, anti-bleeding, iron chelation, and vitamin supplementation).
Comparators	Azacitidine[a] in addition to BSC BSC
Perspective	Canadian publicly funded health care payer
Outcome	Quality-adjusted life-years (QALYs)
Time horizon	Lifetime (50 years)
Key data sources	• The ASCERTAIN trial informed key efficacy and safety parameters of the trial period for decitabine/cedazuridine, with parametric survival analysis used to extrapolate the trial data for overall survival (OS) and acute myeloid leukemia free survival (AML-free survival) over the remainder of the entire model time horizon. • Data from Fenaux et al., and Silverman et al., informed OS and AML-free survival of the trial periods for azacitidine and BSC of the model, respectively, with parametric survival analysis used to extrapolate the trial data for overall survival (OS) and acute myeloid leukemia free survival (AML-free survival) over the remainder of the model time horizon.
Submitted results	• INT-2 to high-risk MDS: ICER = $65,906 per QALY versus BSC (incremental costs: $179,808; incremental QALYs: 2.73)

Component	Description
	• INT-1 MDS: ICER = $61,479 per QALY versus BSC (incremental costs: $231,578; incremental QALYs: 3.77) • CMML: ICER = $74,113 versus BSC (incremental costs: $186,563; incremental QALYs: 2.52) • In all populations azacitidine was subject to extended dominance through decitabine/cedazuridine and BSC.
Key limitations	• The comparative clinical efficacy and safety of decitabine/cedazuridine compared with azacitidine and BSC is highly uncertain. The key efficacy outcomes of the ASCERTAIN trial informing the submitted model (overall survival and AML-free survival) were exploratory, and the sponsor's NMA had several limitations. This included the structure of the networks and potential sources of heterogeneity across trials informing the networks that did not allow the CADTH clinical reviewers and clinical experts to make strong conclusions regarding the comparative efficacy of these treatments. Additionally, there was limited comparative safety information and no comparative information on achievement of transfusion independence. • The sponsor's piecewise modelling approach to estimating the OS and AML-free survival for all comparators constituted a naïve comparison (i.e., non-comparative in nature), leading to survival extrapolations that were associated with substantial uncertainty and did not align with clinical expectations which overestimated potential benefits with decitabine/cedazuridine in comparison with azacitidine and BSC. • The sponsor assumed treatment with azacitidine and decitabine/cedazuridine would be discontinued prior to disease progression, which does not align with its expected use in Canadian clinical practice, underestimating total drug costs. • Risk of developing AML and risk of dying (i.e., OS and AML-free survival) were assumed to be the same, regardless of the health state occupied, for each outcome, respectively. Feedback from the clinical experts consulted by CADTH indicated patients would have a different risk of developing AML and mortality depending on the health state. This adds to the uncertainty of the modelled results. • The majority of the data informing the sponsor's economic submission was for the INT-2 to high-risk subgroup, with limited clinical data including comparative efficacy data in the INT-1 and CMML subgroups.
CADTH reanalysis results	• Due to the limitations associated with the comparative clinical evidence and quality of the submitted model, CADTH could not produce a base case analysis. • CADTH undertook exploratory analyses using alternative efficacy and safety assumptions for decitabine/cedazuridine and azacitidine, and alternate wastage assumptions for azacitidine. • In an exploratory analysis where efficacy, safety and the rate of achieving transfusion independence were assumed to be equal for decitabine/cedazuridine and azacitidine, decitabine/cedazuridine was dominant due to a small QALY benefit (0.01 additional QALYs) due to the disutility associated with azacitidine administration and fewer costs due to assumed additional wastage and administration costs associated with azacitidine. • When no wastage was assumed with azacitidine in addition to equal efficacy, safety and rate of achieving transfusion independence for azacitidine and decitabine/cedazuridine, decitabine/cedazuridine was associated with an ICER above $4.8 million per QALY. A price reduction of over 15% is required for decitabine/cedazuridine to be considered cost-effective in this scenario in the INT-2 to high-risk subgroup. • The lack of robust comparative efficacy data mean the cost-effectiveness of decitabine/cedazuridine in comparison with azacitidine and BSC is unknown.

BSC = best supportive care; CMML – chronic myelomonocytic leukemia; ICER = incremental cost-effectiveness ratio; LY = life-year; MDS = myelodysplastic syndrome; NMA = network meta-analysis; OS = overall survival; PSM = partitioned survival model; QALY= quality-adjusted life-year.

[a] No cost was attributed to BSC within the submission. BSC (as described by the sponsor) was not a component of the trials used to inform decitabine/cedazuridine or azacitidine.

Conclusions

The CADTH Clinical Review determined that due to the limitations with the available comparative evidence – specifically the submitted NMAs – the direction of clinical benefit of decitabine/cedazuridine in comparison with azacitidine with regards to overall survival and AML-free survival is highly uncertain. CADTH's appraisal of the sponsor submitted NMA also suggests the magnitude of benefit for decitabine/cedazuridine compared with BSC for survival outcomes is uncertain. Moreover, as the NMA was predominantly derived from data for the intermediate 2-high risk MDS subgroup, the generalizability of the NMA results to the intermediate 1 MDS and CMML subgroups is highly uncertain. Furthermore, there was limited comparative evidence available for safety and no data for achieving transfusion independence, which were key outcomes informing the model. These limitations led the sponsor to incorporate clinical data in the economic model via a naïve comparison.

As a result of all these limitations, CADTH was unable to determine a base case estimate of the cost-effectiveness of decitabine/cedazuridine for patients with de novo or secondary myelodysplastic syndrome (MDS) who are not considered candidates for hematopoietic stem cell transplantation. As such, CADTH conducted exploratory analyses to assess the impact of alternate clinical data and wastage assumptions. Assuming equal efficacy and safety between decitabine/cedazuridine and azacitidine with regards to OS and AML-free survival, as well as assessing the impact of alternative wastage assumptions with azacitidine. The results of these exploratory analyses ranged from decitabine/cedazuridine being dominant due to a very small gain in QALYs (≤ 0.01) and fewer administration costs, to being associated with an ICER of more than $4.8 million per QALY gained in comparison with azacitidine. These exploratory analyses indicate the model results are very sensitive to the cost assumptions for azacitidine and assumptions regarding the relative treatment effects. Given the limitations with the comparative data, CADTH did not undertake any reanalyses comparing decitabine/cedazuridine with BSC. As such, the cost-effectiveness of decitabine/cedazuridine in comparison with azacitidine and BSC is unknown. The limitations with the sponsor's submitted model and comparative effectiveness data ultimately render the cost-effectiveness of decitabine/cedazuridine in adult patients with de novo or secondary myelodysplastic syndrome (MDS) who are not considered candidates for hematopoietic stem cell transplantation unknown.

Based on the sponsor's submitted budget impact analysis, introducing decitabine/cedazuridine was associated with an estimated cost saving of $[redacted] over the first three years. CADTH reanalyses estimated that the budget impact of introducing decitabine/cedazuridine would result in an increase to drug plan budgets of $3,243,608 in the first three years.

Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 5: Submitted BIA and CADTH Appraisal

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

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