CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ACALABRUTINIB (CALQUENCE)

(AstraZeneca Canada Inc.)

Indication: As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy

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Abbreviations

AE	adverse event
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BEN-RIT	bendamustine plus rituximab
CLL	chronic lymphocytic leukemia
HC	Health Canada
HR	hazard ratio
HTA	Health Technology Assessment
ICER	incremental cost effectiveness ratio
INV	investigator assessed
IDELA-RIT	idelalisib plus rituximab
IRC	independent review committee
IV	intravenous
KM	Kaplan Meier
LY	life year
MAIC	matching adjusted indirect comparison
OS	overall survival
PD	progressed disease
PF	progression free
PFS	progression free survival
PPS	post progression survival
QALY	quality adjusted life year
R/R	relapsed/refractory
TTD	Time To Death
TTNT	Time to Next Treatment
TTP	Time To Progression
VEN-RIT	venetoclax plus rituximab
WTP	Willingness To Pay

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Acalabrutinib (Calquence), Oral capsules
Submitted price	Acalabrutinib, 100 mg, capsule: $135.98 per capsule
Indication	As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
Health Canada approval status	NOC
Health Canada review pathway	Other expedited pathway – Project Orbis
NOC date	November 28, 2019
Reimbursement request	As monotherapy for the treatment of patients with CLL who have received at least one prior therapy.
Sponsor	AstraZeneca Canada Inc.
Submission history	Previously reviewed: No

CLL = chronic lymphocytic leukemia; NOC = Notice of Compliance

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis partition survival model (PSM)
Target population	Patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. This is aligned with the Health-Canada approved indication and sponsor's reimbursement request.
Treatment	Acalabrutinib monotherapy
Comparators	Base case: Ibrutinib Scenario Analysis: • Physician's choice, idelalisib plus rituximab or bendamustine plus rituximab (IDELA-RIT/BEN-RIT) • Idelalisib in combination with rituximab (IDELA-RIT) • Venetoclax in combination with rituximab (VEN-RIT)
Perspective	Canadian publicly funded health care system
Outcomes	QALYs, LYs
Time horizon	Lifetime horizon (15 years)
Key data sources	• PFS and OS curves for acalabrutinib, IDELA-RIT/BEN-RIT and IDELA-RIT were based on the ASCEND trial. • PFS and OS curves for ibrutinib were estimated using patient data from the RESONATE trial. • PFS curve for VEN-RIT was derived from the MURANO trial. • Comparative efficacy for ibrutinib and VEN-RIT was indirectly derived from matching adjusted indirect comparison (MAIC).
Submitted results for base case	• Acalabrutinib was associated with lower costs ($1,187) and higher QALYs (0.13) compared to ibrutinib. ○ The probability of acalabrutinib being cost-effective compared to ibrutinib was 58% at a willingness-to-pay threshold of $50,000 per QALY gained • Compared to IDELA-RIT/BEN-RIT, acalabrutinib resulted in higher costs ($202,075) and higher QALYs (1.49), with an ICER of $135,812 per QALY gained. • Compared to IDELA-RIT, acalabrutinib resulted in higher costs ($216,350) and improved QALYs (1.61) with an ICER of $134,702 per QALY gained. • When compared to VEN-RIT, acalabrutinib was dominated – resulted in higher costs ($268,542) and fewer QALYs (1.26).
Key limitations	• MAIC-derived hazard ratios based on available clinical evidence introduce significant uncertainty into the model that is insufficiently explored and integrated into the economic analysis.
CADTH reanalysis results	• CADTH reanalyses indicated that acalabrutinib was associated with lower costs ($2,644) and higher QALYs (0.12) compared to ibrutinib. These results are closely match those of the sponsor's base case, though this analysis indicates more uncertainty in the probability that acalabrutinib is cost saving compared to ibrutinib. Probabilistic analysis results suggested that, compared to ibrutinib, the probability of acalabrutinib being dominant was 30%, while the probability of acalabrutinib being cost-effective at a WTP threshold of $50,000 per QALY gained was 54%. • Reanalyses also indicated that acalabrutinib remained dominated by VEN-RIT. A price reduction of at least 82% for acalabrutinib is required for VEN-RIT to incur an ICER of $50,000 per QALY compared with acalabrutinib. • CADTH noted the results are highly sensitive to changes in the MAIC-derived HRs and long-term survival outcomes. This finding is concerning given the limitations identified with MAICs led the clinical team to advise using caution to interpret the results. The rest of the model was found to be relatively robust, with minimal significant limitations that would alter cost-effectiveness findings. • CADTH scenario analyses based on the ASCEND trial data indicated that acalabrutinib is associated with an ICER of $142,169 per QALY when compared with IDELA-RIT/BEN-RIT.

BEN-RIT = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; HR = hazard ratio; ICUR = incremental cost-utility; IDELA-RIT = idelalisib; LY = life-year; PSM = partitioned survival model; QALY= quality-adjusted life-year; VEN-RIT = venetoclax plus rituximab; WTP = willingness to pay.

Conclusions

CADTH estimated that acalabrutinib was dominant, i.e., associated with lower total costs and greater QALYs compared to ibrutinib. Compared to ibrutinib, the probability of acalabrutinib being dominant was 55%, while the probability of the treatment being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained was 53%. CADTH identified a higher degree of uncertainty in these findings than in the sponsor's analysis.

Scenario analyses examining the MAIC-derived predicted survival curves and hazard ratios found that the possibility of acalabrutinib being cost-effective was highly sensitive to long-term extrapolation of outcomes and relative effectiveness compared to ibrutinib, meaning that even slight variations in the clinical assumptions impact its predicted outcomes such that acalabrutinib is not always found to be the cost-effective intervention, particularly in the case of ibrutinib. This is largely because the clinical evidence derived from MAICs suggests the efficacy of acalabrutinib is not significantly different from other targeted therapies, including ibrutinib. The comparative efficacy and safety of acalabrutinib compared with VEN-RIT is uncertain due to limitations associated with the MAIC.

CADTH reanalysis results are associated with uncertainty given the identified limitations that could not be addressed, including the lack of head-to-head comparison of acalabrutinib and comparators other than IDELA-RIT/BEN-RIT, limited evidence on PFS and OS data beyond the trial, and concerns about the quality of the submitted MAIC analysis. Based on the head-to-head evidence from the ASCEND trial, acalabrutinib was associated with higher costs and greater QALYs, with ICERs of $142,169 per QALY and $129,522 per QALY when compared to IDELA-RIT/BEN-RIT and IDELA-RIT, respectively.

Based on the sponsor's submitted budget impact analysis, acalabrutinib is estimated to save $[redacted] over the first three years. CADTH reanalyses suggest that the estimated budget impact of introducing acalabrutinib to the market is uncertain due to uncertainty in the estimation of the population size, and assumptions regarding acalabrutinib price and the displacement of less expensive comparators by acalabrutinib. CADTH reanalyses estimated that introducing acalabrutinib to the market may save between $1,960,051 to $2,972,943 over 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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