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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ACALABRUTINIB (CALQUENCE)

(AstraZeneca Canada Inc.)

Indication: With or without obinutuzumab, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) for whom a fludarabine-based regimen is inappropriate.

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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

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CLL	chronic lymphocytic leukemia
HC	Health Canada
HR	hazard ratio
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
INV	investigator assessed
IRC	independent review committee
IV	intravenous
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
TTD	time to death
TTNT	time to next treatment
TTP	time to progression
WTP	willingness to pay

Executive Summary

Table 1: Submitted for Review

Item	Description
Drug product	Acalabrutinib (CALQUENCE), Oral capsules
Submitted price	Acalabrutinib 100 mg, capsule: $135.98 per capsule
Indication	For the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
Health Canada approval status	NOC
Health Canada review pathway	Other expedited pathway – Project Orbis
NOC date	November 28, 2019
Reimbursement request	With or without obinutuzumab, for the treatment of patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate.
Sponsor	AstraZeneca Canada Inc.
Submission history	Previously reviewed: State: No

CLL = chronic lymphocytic leukemia; NOC = Notice of Compliance

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost utility analysis Semi-Markov model
Target population	Elderly (≥65 years) or unfit patients with previously untreated chronic lymphocytic leukemia (CLL). The target population aligns with patients enrolled in the ELEVATE-TN trial and the sponsor's reimbursement request. The target population does not align with the Health Canada approved-indication (all previously untreated CLL patients).
Treatments	Base case: acalabrutinib monotherapy Scenario analysis: acalabrutinib plus obinutuzumab (ACA-OBI)
Comparators	Base case: ibrutinib, chlorambucil plus obinutuzumab (CLB-OBI) Scenario analysis: bendamustine plus rituximab (BEN-RIT)
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life years (QALYs), Life years (LYs)
Time horizon	20 years
Key data sources	• ELEVATE-TN trial was used to inform acalabrutinib monotherapy, ACA-OBI and CLB-OBI. • MAICs were used to derive HRs to inform the comparisons with ibrutinib and BEN-RIT. • Data from the MURANO and RESONATE trials were used to inform PPS for subsequent treatments.

Submitted results for base case	• The sponsor's sequential analysis indicated that acalabrutinib monotherapy was associated with higher costs ($237,754) and higher QALYs (2.79) compared to CLB-OBI, with an ICER of $85,147 per QALY. Ibrutinib was dominated by acalabrutinib monotherapy ($65,624 more costly, 0.06 fewer QALYs).
	• Pairwise scenario analyses indicated ACA-OBI had an ICER of:
	  ○ $58,563 per QALY compared to CLB-OBI
	  ○ $104,959 per QALY compared to ibrutinib.

Key limitations	• Comparative efficacy for acalabrutinib with and without obinutuzumab when compared with ibrutinib monotherapy and BEN-RIT was derived from multiple MAICs. The CADTH clinical review highlighted several concerns about the internal validity of MAIC results given the substantial heterogeneity in the populations included, differences in effect modifiers, and in the design of included studies. • The submitted model applied fixed TTP and TTD curves based on PFS and OS, and these curves have integrated relative hazards between interventions making it impossible to perform crucial scenario analyses or test structural uncertainties with the model.
CADTH reanalysis results	• CADTH reanalyses considered corrections to the sponsor's model and alternate cost sources. • Compared to CLB-OBI, acalabrutinib monotherapy is associated with higher costs ($147,524) and higher QALYs (2.25), resulting in an increase ICER to $65,672 per QALY. The probability that acalabrutinib is cost-effective was 37% at the WTP of $50,000 per QALY. • A sequential scenario analysis incorporating ACA-OBI into the above analysis indicated that ACA-OBI is dominated by acalabrutinib monotherapy. • These findings are consistent with the CADTH clinical review findings suggesting ACA-OBI is similarly effective to acalabrutinib monotherapy but associated with greater toxicity, and that acalabrutinib with or without obinutuzumab is associated with greater PFS benefit compared to CLB-OBI. • Acalabrutinib monotherapy is dominant when compared to main comparator of interest, ibrutinib (due to fewer costs and similar QALYs). • The cost-effectiveness estimates are sensitive to the assumptions around PFS and OS. Given the methodological limitations with the MAICs and limitation with the model structure, the results for acalabrutinib compared with ibrutinib should be viewed with caution.

ACA-OBI = acalabrutinib plus obinutuzumab; BEN-RIT = bendamustine plus rituximab; CLB-OBI = chlorambucil plus obinutuzumab; CLL = chronic lymphocytic leukemia; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching adjusted indirect comparison; QALY= quality-adjusted life-year; TTP = time to progression; TTD = time to death; WTP = willingness to pay.

Conclusions

The CADTH clinical review found that there is a net clinical benefit with the use of acalabrutinib, as monotherapy or in combination with obinutuzumab in patients with previously untreated CLL who are 65 years or older, or adults younger than 65 with significant comorbidities when compared to CLB-OBI, based on evidence from the ELEVATE-TN trial. The clinical review also concluded that acalabrutinib monotherapy may be preferred to ACA-OBI use as it demonstrated similar efficacy with considerably less toxicity. The relative effectiveness against a more appropriate comparator, e.g. ibrutinib, is uncertain due to significant limitations with the submitted indirect comparison via matching-adjusted indirect comparison (MAIC).

Given these clinical findings, the cost-effectiveness of acalabrutinib, as monotherapy or in combination with obinutuzumab, in patients with previously untreated CLL who are fludarabine-eligible is unknown given the lack of clinical evidence for the use of acalabrutinib in that patient population. Furthermore, CADTH was unable to undertake sequential analyses that included the most relevant comparator currently available (ibrutinib) due to the nature of the clinical comparisons submitted by the sponsor – multiple MAICs. These MAICs were associated with methodological uncertainty, such that any differences between treatments are associated with unknown magnitude.

CADTH identified several limitations with the model design and clinical data that could not be addressed, and thus the reported results should be interpreted with caution. The comparison of acalabrutinib monotherapy with CLB-OBI (and ACA-OBI) uses the best available data from the ELEVATE-TN trial. The results of this analysis suggests that acalabrutinib monotherapy is more effective and more costly than CLB-OBI (ICER = $65,672 per QALY), and associated with greater QALYs and fewer costs compared with ACA-OBI (i.e., dominant). The clinical outputs from the model are aligned with the findings of the CADTH clinical review. A price reduction of at least 4% is required to achieve an ICER of $50,000 per QALY for acalabrutinib monotherapy compared with CLB-OBI.

Based on the sponsor's submitted budget impact analysis, the total incremental cost for the population that aligns with the best clinical data (i.e., previously untreated CLL patients who are fludarabine ineligible per the reimbursement request population) was estimated to be $[redacted] over the first three years. CADTH noted that the analyses are sensitive to parameters for which there of limited information: population size, assumptions regarding treatment uptake, and treatments most likely to be displaced, as well as the price of acalabrutinib. CADTH's reanalyses suggest that the estimated budget impact of introducing acalabrutinib to the market is uncertain due to discrepancies in the estimation of the population size, and assumptions regarding ACA-OBI use, acalabrutinib price, and the displacement of ibrutinib by acalabrutinib and the treatments most likely to be displaced. CADTH reanalyses indicated that the three-year budget impact of introducing acalabrutinib to the market may range from $225,335 to $400,259 in this population. If the population is expanded to all previously untreated CLL patients, the budget impact may increase to between $336,321 to $597,402.

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

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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.

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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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