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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

BLINATUMOMAB (BLINCYTO)

AMGEN

Indication: For the treatment of patients with Philadelphia chromosome-negative, CD19-positive, B-cell precursor acute lymphoblastic leukemia in first or second hematologic complete remission with minimal residual disease greater than or equal to 0.1%.

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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, diagnos ics, 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

ATE	average treatment effect
ATT	average treatment effect on the treated
BCP-ALL	B-cell precursor acute lymphoblastic leukemia
CDR	CADTH Common Drug Review
HSCT	Hematopoietic stem cell transplant
ICER	incremental cost-effectiveness ratio
IO	inotuzumab ozogamicin
LY	life years
MRD	minimal residual disease
Ph-	Philadelphia chromosome-negative
QALY	quality-adjusted life-year
SOC	standard of care

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	blinatumomab (Blincyto), 38.5 mcg of lyophilized powder for solution for infusion
Submitted price	blinatumomab, lyophilized powder: $2,978.26 per 38.5 mcg vial
Indication	Adult and pediatric with Philadelphia chromosome-negative (Ph-) CD19+ B-cell precursor acute lymphoblastic leukemia (BCP-ALL) in first or second hematologic complete remission with minimal residual disease greater than or equal to 0.1% (MRD+). Patients are to be selected for treatment based on detection of MRD as determined by an accredited laboratory using validated assay methods.
Health Canada approval status	NOC/c
Health Canada review pathway	NOC/c
NOC date	Dec 19, 2019
Reimbursement request	As per indication
Sponsor	Amgen Canada Inc.
Submission history	Previously reviewed: Yes Indication: Adults with relapsed or refractory Ph- BCP-ALL Recommendation date: 09/31/2017 Recommendation: Reimburse with price reduction
	Previously reviewed: Yes Indication: Children with relapsed or refractory Ph- BCP-ALL Recommendation date: 09/23/2017 Recommendation: Reimburse with price reduction

BCP-ALL = B-cell precursor acute lymphoblastic leukemia; MRD+ = minimal residual disease greater than or equal to 0.1%; NOC/c = Notice of Compliance with conditions; Ph- = Philadelphia chromosome-negative

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	Adults (≥18 years) with Philadelphia chromosome-negative (Ph-) B-cell precursor acute lymphoblastic leukemia (BCP-ALL) with minimal residual disease (MRD+) in first complete remission [a]
Treatment	Blinatumomab
Comparator	Standard of care (SOC; Dana-Farber Cancer Institute protocol for multi-agent chemotherapy)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data source	Studies MT103-203 (BLAST), 20120148 (historical comparator), NCT02013167 (TOWER)
Submitted results for base case	Base case: adult patients with MDR+ Ph- BCP-ALL in first hematological complete remission • ICER = $33,180 per QALY (incremental cost = $111,333; incremental QALYs = 3.36)
Key limitations	• The modeled population was restricted to adults in first complete remission and did not address the Health Canada indication for children with MRD+ Ph- BCP-ALL or for adults in second complete remission. A scenario analysis was conducted to estimate the cost-effectiveness of blinatumomab in the pediatric population with MRD+ Ph- BCP-ALL but this was based entirely on adult data and was therefore not appropriate. Compared with SOC, blinatumomab's cost-effectiveness for the pediatric population and for adults in second complete remission remains unknown. • The impacts of certain structural uncertainties in the semi-Markov model could not be explored. The model only explicitly linked HSCT to cure in those patients who received HSCT prior to relapse and did not incorporate the effects on relapsed patients. • The number of in-patient hospital days for treatment with blinatumomab and within the pre-relapse health state did not reflect clinical practice in Canada. The clinical experts consulted by CADTH for this review expected the frequencies to be higher for all treatment cycles and lower for the pre-relapse health state. • The use of 20-year-old data for HSCT relate parameters (e.g., patient eligibility for HSCT, access to HSCT, or clinical decisions to perform HSCT within existing clinical practice) is unlikely to reflect current practice and, therefore, introduced considerable uncertainty in the time to HSCT modeled for SOC. • The distribution of patients with relapsed disease who received conventional multi-agent chemotherapies versus a newer approved therapy, inotuzumab ozogamicin, had limited clinical plausibility.
CADTH reanalysis results	The CADTH reanalyses reflected revised inputs for: the frequencies of in-patient hospital days; the time to treatment with HSCT for the SOC comparator; and, the distribution of treatments among all patients who relapsed. CADTH was unable to address limitations concerning excluded subgroups and structural uncertainties within the submitted model. ICER: $118,234 per QALY gained ($112,322 incremental costs, 0.95 incremental QALYs) compared with SOC, for adults in first hematologic complete remission. • CADTH noted the results generated warrant careful interpretation since the likelihood blinatumomab was cost-effective at a willingness-to-pay threshold of $100,000 per QALY was 43% and only 16% at a threshold of $50,000 per QALY. • To achieve an ICER below $50,000 per QALY gained, blinatumomab's price would need to be reduced by 42%. • The cost-effectiveness of blinatumomab compared to SOC for children with MRD+ Ph- BCP-ALL in first or second complete remission, and for adults in second complete remission, is unknown.

BCP-ALL = B-cell precursor acute lymphoblastic leukemia; HSCT = hematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; LY = life-year; MRD+ = minimal residual disease greater than or equal to 0.1%; Ph- = Philadelphia chromosome-nega ive; QALY= quality-adjusted life-year; SOC = standard of care

[a] The Health Canada indication and reimbursement request comprised of adults and children with MRD+ Ph- BCP-ALL. Patients are to be selected for treatment based on the detection of MRD as determined by an accredited laboratory using validated assay methods.

Conclusions

CADTH undertook reanalyses to address limitations relating to the application of in-patient hospital days, the time to treatment with hematopoietic stem cell transplant (HSCT) for the standard of care (SOC) comparator, and the distribution of treatments among all patients who relapsed.

Based on CADTH's reanalysis for a subgroup of the Health Canada indication (adults in first complete remission), the ICER for blinatumomab versus SOC was estimated to be $118,234 per additional QALY gained. A reduction of at least 42% in blinatumomab's price was required to improve its cost-effectiveness, relative to SOC, and generate an ICER that was less than $50,000 per QALY. These results were based on 20-year-old, matched data on the risk of relapse for the SOC comparator. The use of these data likely underestimates the effectiveness of current SOC chemotherapies and was shown to be a notable source of uncertainty in CADTH's exploratory analyses. Therefore, the presented ICER likely represents an underestimation of the true ICER for blinatumomab compared with SOC. Additional scenario and exploratory analyses were undertaken, which highlighted that the uncertainty associated with the use of 20-year-old data on the risk of relapse for the SOC comparator.

The results of CADTH's reanalysis were restricted to adults in first complete remission and remain uncertain as multiple limitations could not be addressed. CADTH was unable to assess the cost-effectiveness of blinatumomab compared to SOC for the full Health Canada indication. As such, the cost effectiveness of blinatumomab for children with MRD+ Ph- BCP-ALL in first or second complete remission and for adults in second complete remission is unknown.

Based on the sponsor's submitted budget impact analysis, the total incremental budget impact was estimated to be $16,508,161 over three years for adults and children MDR+ Ph- BCP-ALL in hematological complete remission in Canada. CADTH identified limitations in the sponsor's approach for capturing the impacts of post-relapse drug costs. In the CADTH reanalysis, the total budget impact over the 3-year horizon was $24,229,491.

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.

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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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