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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

BRENTUXIMAB VEDOTIN (ADCETRIS)

(Seattle Genetics, Inc.)

Indication: Adult patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have had prior systemic therapy

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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
alloSCT	allogeneic stem cell transplantation
ASCT	autologous stem cell transplant
BIC	Bayesian information criterion
BV	brentuximab vedotin
CDR	CADTH Common Drug Review
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
KM	Kaplan-Meier
LY	life-year
MF	mycosis fungoides
mg	milligram
NOC	Notice of Compliance
OS	overall survival
PC	physician's choice
pcALCL	primary cutaneous anaplastic large cell lymphoma
PFS	progression-free survival
PROCLIPI	Prospective Cutaneous Lymphoma International Prognostic Index
QALY	quality-adjusted life-year
TOT	time off treatment
USP	United States Pharmacopeia

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	Brentuximab vedotin (Adcetris), lyophilized powder for reconstitution with 10.5 mL of sterile water for injection, USP 50 mg
Submitted price	Brentuximab vedotin, 50 mg, lyophilized powder: $4,840 per 50 mg vial
Indication	Adult patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have had prior systemic therapy.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	December 21, 2018
Reimbursement request	As per indication
Sponsor	Seattle Genetics, Inc.
Submission history	Previously reviewed: Yes Indication: Hodgkin's Lymphoma at high risk of relapse or progression post-ASCT Recommendation date: February 21, 2018 Recommendation: Recommended with clinical criteria; a substantial reduction in drug price would likely be required.

ASCT = autologous stem cell transplant; NOC = Notice of Compliance; USP = United States Pharmacopeia

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have had prior systemic therapy.
Treatment	Brentuximab vedotin (BV)
Comparator	Physician's choice (PC), methotrexate or bexarotene
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (45 years)
Key data source	ALCANZA study
Submitted results for base case	ICER = $20,637 per QALY gained (incremental cost = $6,025; incremental QALYs = 0.29)
Key limitations	• The modeled comparator, physician's choice, is a blended comparator of methotrexate and bexarotene, which does not reflect Canadian practice since bexarotene is rarely prescribed. Further, other relevant comparators (e.g., interferon-alphas) were not considered. • Data used to model the effects of supplementary alloSCT were obtained from patients who were substantially different to the modeled population as per the ALCANZA trial. • According to the clinical expert consulted by CADTH, key features of the treatment pathway following relapsed disease are not reflective of expected clinical practice. These included the use of BV as a subsequent therapy for relapsed patients (particularly among those who did not receive alloSCT) and the different durations of end-stage care for different treatment comparators. • Although the sponsor accounted for vial wastage using a method of moments approach, the sponsor also applied the relative dose intensity observed within ALCANZA for BV (95% of the recommended dose per kg) which decreased the number of BV vials required. According to the clinical expert consulted by CADTH, this approach underestimated the drug acquisition cost of BV as the quantity of BV vials dispensed within practice would likely be made according to dose recommendations outlined within the product monograph. • The sponsor incorporated expert-elicited frequencies of resource use that did not align with Canadian clinical practice based on feedback from the clinical expert. • The sponsor assumed that no OS benefit was associated with BV compared with PC in patients who did not receive alloSCT given the immaturity of OS data in ALCANZA.[a] The implication of assuming no OS benefit for BV in patients that who do not receive alloSCT is that patients receiving BV die more quickly upon progression compared with PC and incur lower health care costs associated with progression than if the length of post-progression survival was equal between patients receiving BV and PC. This was not expected to reflect clinical practice according to the clinical experts consulted by CADTH.
CADTH reanalysis results	CADTH as part of its reanalysis, revised the proportion of treatment responders that received alloSTC within the treatment pathway and BV as a subsequent therapy; revised the length of end-stage care to be the same for all patients; and, revised resource use frequencies and relative dosing intensities. CADTH was unable to address the other identified limitations in reanalyses. ICER: $1,266,378 per QALY gained ($96,492 incremental costs, 0.08 incremental QALYs) compared with a blended comparator of methotrexate and bexarotene. • CADTH noted that the results in the indicated population warrant careful interpretation as BV was associated with 0.37 fewer QALYs than PC during the trial period and 0.45 additional QALYS than PC during the extrapolated period (i.e., 590% of the total 0.08 incremental QALYs were accrued during the extrapolation period). • A price reduction of 64% is required for BV to be considered cost-effective at a WTP threshold of $50,000 per QALY gained.

Component	Description
	• The cost-effectiveness of BV relative to individual treatments such as methotrexate or bexarotene, or excluded comparators (e.g., interferon-alphas) is unknown.

alloSTC = allogeneic stem cell transplant; BV = brentuximab vedotin; ICER = incremental cost-effectiveness ratio; LY = life-year; MF = mycosis fungoides; PC = physician's choice; pcALCL = primary cutaneous anaplastic large cell lymphoma; QALY= quality-adjusted life-year; WTP = willingness-to-pay

[a] Although the sponsor assumed that no OS benefit was associated with BV compared with PC in patients who did not receive alloSCT, the total expected survival reported for these patients in Table 3 (sponsor's base case results) differed. For example, total life-years accrued in the pre-progression and post-progression health states for those who did not receive alloSCT was 8.13 for BV (1.89+6.04+0.20) and 8.71 for PC (0.65+7.64+0.42). The reason for this difference was that a greater proportion of patients on BV than PC were modeled to receive alloSCT (BV = 10%; PC = 3%), which was assumed to be associated with a survival benefit.

Conclusions

To address identified limitations with the sponsor's economic model, CADTH: adjusted the proportions who received alloSTC in the treatment pathway; modified the proportion of treatment responders who received BV as a subsequent therapy; revised the length of end-stage care to be the same for all patients; and, revised resource use frequencies and relative dosing intensities. In the CADTH base case, the ICER for BV compared with a blended comparator of methotrexate and bexarotene (i.e. Physician's Choice (PC)) was $1,266,378 per QALY gained. The probability that BV was cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained was 0%. A price reduction of at least 64% is required for BV to be considered cost-effective at a WTP threshold of $50,000 per QALY gained, compared with PC.

The application of sponsor-submitted proportions of partial and complete responders who should receive alloSCT in separate scenario analyses resulted in ICERs of $357,664 per QALY gained (15% of responders receive alloSCT) and $819,127 per QALY gained (5% of responders receive alloSCT), further suggesting that BV compared with PC was not cost-effective at WTP thresholds of $50,000 or $100,000 per QALY gained.

CADTH was unable to address limitations associated with the PC comparator (i.e., the combination of methotrexate and the rarely prescribed bexarotene, as opposed to modelling each treatment individually) and the exclusion of other relevant comparators (e.g., interferon-alphas). As such the cost-effectiveness of BV relative to these comparators is unknown. Furthermore, the majority of BV's incremental benefit (590% of the total 0.08 incremental QALYs) was accrued beyond the trial period for which data was available, casting further uncertainty on the clinical and cost-effectiveness of BV.

Based on the sponsor's submitted budget impact analysis, the total incremental cost was estimated to be $10,569,101 over the first three years. CADTH's reanalysis suggests that the estimated budget impact of introducing BV to the market was underestimated in the sponsor's budget impact analysis. The total incremental cost of introducing BV to the market in the CADTH re-analysis is estimated $34,475,075 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.

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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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