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CADTH DRUG REIMBURSMENT REVIEW

Pharmacoeconomic Report

BRENTUXIMAB VEDOTIN (ADCETRIS)

(Seattle Genetics)

Indication: For the treatment of previously untreated adult patients with systemic anaplastic large cell lymphoma, peripheral T-cell lymphoma-not otherwise specified or angioimmunoblastic T-cell lymphoma, whose tumours express CD30 in combination with cyclophosphamide, doxorubicin, and prednisone

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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

A+CHP	brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone
AE	adverse event
AIC	Akaike Information Criteria
AITL	angioimmunoblastic T-cell lymphoma
ATLL	adult T-cell leukemia or lymphoma
BIA	budget impact analysis
BIC	Bayesian Information Criteria
BSA	body surface area
BV	brentuximab vedotin
CAD	Canadian Dollars
CGP	clinical guidance panel
CD30	cluster of differentiation 30
CHOEP	cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHP	cyclophosphamide, doxorubicin, and prednisone
EATL	enteropathy-associated T-cell lymphoma
EQ-5D	European Quality of Life Five Dimensions
ICER	incremental cost-effectiveness ratio
HR	hazard ratio
IV	intravenous
KM	Kaplan-Meier
LY	life year
OS	overall survival
PAG	Provincial Advisory Group
pCODR	CADTH pan-Canadian Oncology Drug Review
PFS	progression-free survival
PPS	post-progression survival
PTCL	peripheral T-cell lymphoma
PTCL NOS	peripheral T-cell lymphoma not otherwise specified
QALY	quality-adjusted life year
sALCL	systemic anaplastic large cell lymphoma
SCT	stem cell transplant
WTP	willingness-to-pay

Executive Summary

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

Table 1: Submitted for Review

Item	Description
Drug product	Brentuximab vedotin (Adcetris), 50mg vial
Submitted price	Brentuximab vedotin, 50mg vial: $4,840
Indication	For the treatment of previously untreated adult patients with systemic anaplastic large cell lymphoma, peripheral T-cell lymphoma-not otherwise specified or angioimmunoblastic T-cell lymphoma, whose tumours express CD30, in combination with cyclophosphamide, doxorubicin, and prednisone
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	22 Nov 2019
Reimbursement request	As per indication
Sponsor	Seattle Genetics, Inc
Submission history	Previously reviewed: No

CD30 = cluster of differentiation 30; NOC = Notice of Compliance; PTCL= peripheral T-cell Lymphoma; CHP = cyclophosphamide, doxorubicin, and prednisone

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Previously untreated adult patients with systemic anaplastic large cell lymphoma (sALCL), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) or angioimmunoblastic T-cell lymphoma (AITL), whose tumours express CD30, in combination with cyclophosphamide, doxorubicin, and prednisone (aligned with reimbursement request)
Treatment	Brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (A+CHP)
Comparator	Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (45 years)
Key data source	ECHELON-2 trial reporting overall survival (OS) and progression-free survival (PFS)
Submitted results for base case	ICER = $32,470 per QALY (2.32 inc. QALYs; $75,444 inc. costs)
Key limitations	• The sponsor omitted CHOEP as comparator in its base case analysis. They did, however, include it as scenario analysis upon request. • The patient populations were heterogeneous in terms of histological subtypes resulting in survival differences across subtypes which are expected to have an impact on the cost-effectiveness of A+CHP. The sponsor's submission did not allow stratification by histological subtype, but provided a separate model for the sALCL subtype upon CADTH's request. The cost-effectiveness for patients with PTCL-NOS subtype and AITL subtypes is unknown. • There was significant uncertainty regarding long-term extrapolation as OS data was not mature and short-term data (median follow-up of 36 months) was used to extrapolate long-term benefits throughout the lifetime horizon (i.e., 45 years), resulting in an increased risk for an overestimation of patient survival. Furthermore, as long-term OS extrapolations resulted in survival higher than the general population, the sponsor replaced extrapolated OS with general population survival rates. The assumption that survival in these patients would at some point reach that of the general population was felt unrealistic by clinical guidance panel. • Health utility values used in the sponsor's model were based on the EQ-5D from the ECHELON-2 trial. The sponsor used US weights (value set) in the analysis and as such utility values may not reflect the preferences of Canadian patients. Furthermore, utility values are likely overestimated as values for the progression-free state are very close to the value estimated in the general population of healthy Canadians. • Treatment-specific disutilities for AE were not included in the sponsor's base case. AE disutilities for grade 3 and 4 AEs were included in a scenario analyses, excluding AEs considered clinically meaningful to clinical experts and patient groups consulted by CADTH. • The sponsor's model structure did not explicitly consider stem cell transplantation (SCT). Since patients undergoing STC may have longer survival than patients without SCT, SCT should have been modeled separately in order to assess the impact of varying SCT rates on the overall cost-effectiveness of A+CHP.
CADTH reanalysis results	CADTH reanalyses included: inclusion of CHOEP as comparator, alternative long-term extrapolations, inclusion of increased non-cancer mortality, use of UK weights for utilities, inclusion of AE-specific disutilities, and a revised time horizon of 42 years. Since CHOEP was assumed to have the same efficacy as CHOP, only pairwise comparisons were relevant. ICER (A+CHP vs CHOP) = $79,319 per QALY (0.94 inc. QALYs; $74,212 inc. costs) ICER (A+CHP vs CHOEP) = $72,991 per QALY (0.94 inc. QALYs; $68,473 inc. costs) A reduction of approximately 35% and 30% in the price of brentuximab vedotin would be required to bring the ICER around $50,000 per QALY compared to CHOP and CHOEP, respectively.

A+CHP = Brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone; AITL = angioimmunoblastic T-cell lymphoma; CD30 = cluster of differentiation 30; CHOP = Cyclophosphamide, doxorubicin, vincristine, and prednisone; ICER = incremental cost-effectiveness ratio; LY = life-year; NOS = not otherwise specified; PTCL = peripheral T-cell Lymphoma; QALY= quality-adjusted life-year; sALCL = systemic anaplastic large cell lymphoma;

Conclusions

CADTH undertook reanalyses of the sponsor's economic submission to address some of the identified limitations, i.e., the inclusion of CHOEP as comparator (assuming same efficacy as CHOP), alternative long-term extrapolations, inclusion of increased non-cancer mortality, the use of UK value set applied to EQ-5D collected during the ECHELON-2 trial, the inclusion of AE-specific disutilities, and a revised time horizon of 42 years (i.e., until the cohort reaches 100 years old). Following CADTH reanalysis, the ICER of A+CHP compared to CHOP was estimated to be $79,319 per QALY gained, whereas the ICER of A+CHP compared to CHOEP was $72,991 per QALY gained. A reduction of approximately 35% and 30% in the price of brentuximab vedotin would be required to bring the ICER around $50,000 per QALY.

Some identified limitations could not be addressed by CADTH (e.g., impact of a different proportion of patients undergoing consolidative stem cell transplant, impact of grade 1 and 2 AEs relevant to patients) or could only be addressed through exploratory analysis (e.g., heterogeneity of outcomes across PTCL-NOS and AITL subtypes) due to lack of data. The sponsor provided a separate model for the sALCL subtype upon CADTH's request. However, the model provided by the sponsor for this subtype was different from the model provided for the overall population, and as such CADTH was unable to perform all reanalysis in line with the CADTH base case.

Based on the sponsor's submitted budget impact analysis, the total incremental cost is estimated to be $39,812,976 over the first 3 years. CADTH reanalysis suggests that the budget impact of introducing A+CHP to the market was underestimated in the sponsor's results and estimated to be $72,999,332 over the first 3 years in CADTH reanalysis.

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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