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CADTH REIMBURSEMENT REVIEW

Pharmacoeconomic Report

Polatuzumab Vedotin (POLIVY)

(Hoffmann-La Roche Limited)

Indication: In combination with bendamustine and rituximab for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, who are not eligible for autologous stem cell transplant and have received at least one prior 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

AE	adverse event
ASCT	autologous stem cell transplant
BSA	body surface area
CAR-T	chimeric antigen receptor T-cell
CEAC	cost effectiveness acceptability curve
CEOP	rituximab + cyclophosphamide + etoposide + vincristine + prednisone
CEPP/PEP-C	prednisone + etoposide + procarbazine + cyclophosphamide
CHOP	prednisone + cyclophosphamide + doxorubicin + vincristine
CVP	cyclophosphamide + vincristine + prednisolone
DHAP	dexamethasone + cisplatin + cytarabine
DICEP	dose-intensive cyclophosphamide + etoposide + cisplatin
DLBCL	diffuse large B-cell lymphoma
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin
GDP	gemcitabine + dexamethasone + cisplatin
GEMOX	gemcitabine + oxaliplatin
ICE	ifosfamide + cisplatin or carboplatin + etoposide
OS	overall survival
PFS	progression-free survival
QALY	quality-adjusted life year
RWD	real-world data
WTP	willingness to pay

Executive Summary

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

Table 1: Submitted for Review

Item	Description
Drug product	Polatuzumab vedotin (Polivy), vial for intravenous (IV) infusion
Submitted price	Polatuzumab vedotin: $14,750.00 per 140 mg vial
Indication	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, who are not eligible for autologous stem cell transplant and have received at least one prior therapy
Health Canada approval status	NOC/c
Health Canada review pathway	Advance consideration under NOC/c
NOC date	July 09, 2020
Reimbursement request	As per indication.
Sponsor	Hoffmann-La Roche Limited
Submission history	Previously reviewed: No

IV, intravenous; NOC/c = Notice of Compliance with Conditions

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), not otherwise specified, who are not eligible for autologous stem cell transplant and have received at least one prior therapy.
Treatments	Polatuzumab vedotin + bendamustine + rituximab (Pola-BR)
Comparators	Basket of treatment regimens ("basket comparator") used in Canadian practice as reflected by the Alberta O2 real-world dataset. These regimens include: R-GDP, R-DICEP, Dexa-Etop, pembrolizumab, PEP-C, R-CEOP, BP, R-Ino, R-BV
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data source	Relative effects of pola-BR for PFS and OS compared to a basket comparator: a propensity score method was applied to individual participant data from the GO29365 trial (N=91) and the Alberta O2 real-world data (RWD) registry (N=42)

Submitted results for base case and key scenario analyses	• Base-case analysis: pola-BR was associated with an ICER of $57,711 per QALY ($122,932 incremental costs, 1.750 incremental QALYs) compared to the basket comparator.
	• Scenario analyses: Pola-BR was:
	  ○ associated with an ICER of $58,909 per QALY when compared with BR,
	  ○ dominant (less costly and more effective) compared to tisagenlecleucel,
	  ○ less costly and less effective than axicabtagene ciloleucel.

Key limitations	• The comparative efficacy of pola-BR and the basket comparator is highly uncertain. Given the lack of direct evidence, the sponsor derived the comparative efficacy using a propensity score matching analysis approach. CADTH identified major limitations related to the size of the cohort used, the ability to efficiently weight between RWD and trial data, and the differences between study arms. This introduced significant uncertainty into the indirect comparison that could not be sufficiently accounted for within the submitted economic analysis, and any analyses based on these data must be viewed with caution. • The sponsor pooled the efficacy data for pola-BR from different patient cohorts within the GO29365 trial. CADTH identified concerns with the data pooling such as notable differences in the trial design that may introduce (methodological and clinical) heterogeneity between cohorts. Without proper adjustment for the heterogeneity, pooling these cohorts may introduce biases into the results. • The clinical experts consulted on this review suggested that the predicted survival rates in the sponsor's model, especially for patients with progressed disease, were overestimated and not aligned with the observed and expected survival for this patient population. • CADTH identified errors in the sponsor's model: including use of a non-approved vial size (30 mg), excluding SEB price for rituximab, including anti-CD20 use as subsequent treatment, and using a small number of iterations. CADTH was able to correct for these errors.
CADTH reanalysis results	• Due to the limitations identified with the sponsor's model, including the available data and model mechanics, CADTH could not determine a CADTH base case. • To provide a more credible analysis prior to exploring different scenarios for the clinical data, the sponsor's corrected based case resulted in an ICER of $70,264 per QALY. • Based on CADTH's exploratory analyses examining different assumptions regarding the clinical data, the cost-effectiveness of Pola-BR could range from $67,000 per QALY to $147,000 per QALY compared with the basket comparator. However, there is substantial uncertainty associated with these estimates, given the limitations identified with the comparative clinical information.

BP = bendamustine + prednisone; CAR-T = chimeric antigen receptor T-cell therapy; Dexa-Etop = dexamethasone + etoposide; ICER = incremental cost-effectiveness ratio; LY = life-year; PEP-C = prednisone + etoposide + procarbazine + cyclophosphamide; Pola-BR = polatuzumab vedotin + bendamustine + rituximab; QALY= quality-adjusted life-year; R-BV = rituximab + brentuximab vedotin; R-CEOP = rituximab + cyclophosphamide + etoposide + vincristine + prednisone; R-DICEP = rituximab + dose-intensive cyclophosphamide + etoposide + cisplatin; R-GDP = rituximab + gemcitabine + dexamethasone + cisplatin; R-Ino = rituximab + inotuzumab ozogamicin; RWD = real world data; SEB = subsequent entry biologic.

Conclusions

Due to the lack of direct clinical evidence comparing pola-BR to current standard of care used in Canada, the sponsor derived comparative effectiveness estimates from the GO29365 trial and Alberta real-world database using a propensity score matching analysis approach. CADTH identified major limitations with this analysis, and determined that no firm conclusions could be drawn on the comparative effectiveness of pola-BR compared with the basket comparator. CADTH was unable to address several major limitations, including the lack of direct evidence on comparative clinical data with comparators indicated and used in Canadian clinical practice, the use of a basket comparator of nine currently used treatments for r/r DLBCL, and substantial uncertainty residual confounders from the submitted propensity score analysis.

The issues with the clinical data prohibit a reasonable assessment of cost-effectiveness. As such, a CADTH base case could not be derived. CADTH undertook reanalyses to correct the sponsor's base case by using an approved vial size (140 mg) of polatuzumab, applying SEB price for rituximab, removing anti-CD20 use as subsequent treatment, and increasing the number of simulations, as well as present a series of exploratory analyses to highlight the uncertainty associated with the sponsor's ICER. When correcting for available vial size of pola-BR, using appropriate costs for rituximab, and increasing iterations to reduce variance in the ICER, pola-BR was associated with ICER of $70,264 per QALY compared to the basket comparator. CADTH undertook a series of exploratory reanalyses which suggested that the ICER of pola-BR was likely to be higher than estimated by the sponsor; when focusing on just the reanalyses based on alternate clinical data assumptions, the ICER for pola-BR compared with the basket comparator ranged from $67,000 per QALY to $147,000 per QALY. However, all of these results suggest that pola-BR controls the disease better than a basket comparator post-progression which was considered hypothetical and without biological support by clinical experts consulted by CADTH. The exploratory analyses resulting in higher ICERs are due to fewer incremental life years and QALYs being accrued in the post-progression state. Based on these exploratory analyses, a price reduction for polatuzumab of between 35% and 84% would be required for pola-BR to become cost-effective at a WTP threshold of $50,000 per QALY compared with the basket comparator, however, the uncertainty identified with the comparative clinical information and modelling approach suggest caution when interpreting these results.

Based on the sponsor's submitted budget impact analysis, the total budget impact of reimbursing pola-BR under the full Health Canada indication was estimated to be $[redacted] over the first three years. CADTH re-analysis of the sponsor's submitted BIA suggests that the estimated budget impact of introducing pola-BR would be $66,588,692 over the first 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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