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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ISATUXIMAB (SARCLISA)

(Sanofi Genzyme)

Indication: In combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

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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
AE	adverse events
BIC	Bayesian information criterion
CD-38	cluster of differentiation 38 (cyclic ADP ribose hydrolase)
CycloPd	cyclophosphamide in combination with pomalidomide plus dexamethasone
EQ-5D-5L	Euroqol-5 dimension-5 level
ICER	incremental cost-effectiveness ratio
IsaPd	isatuximab in combination with pomalidomide plus dexamethasone
Kd	carfilzomib plus dexamethasone
OS	overall survival
Pd	pomalidomide plus dexamethasone
PFS	progression-free survival
PSM	partition-survival model
QALY	quality-adjusted life-years
RDI	relative dosing intensity
RRMM	relapsed and/or refractory multiple myeloma
TTD	time-to-treatment discontinuation
WTP	willingness to pay

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	Isatuximab (Sarclisa), solution for injection (20 mg/mL), 100 mg or 500 mg single-use vial
Submitted price	Isatuximab, 6 mL (100 mg / 5 mL), intravenous injection: $757.90 Isatuximab, 30 mL (500 mg / 25 mL), intravenous injection: $3,789.49
Indication	Isatuximab in combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	April 29, 2020
Reimbursement request	As per indication
Sponsor	Sanofi-Aventis Canada Inc.
Submission history	Previously reviewed: No

mg – milligrams; mL = milliliters; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with relapse and/or refractory multiple myeloma who have received two or more prior therapies, including lenalidomide and a proteasome inhibitor
Treatment	Isatuximab in combination with pomalidomide + dexamethasone (IsaPd)
Comparator	Pomalidomide + dexamethasone (Pd)
Perspective	Canadian publicly funded health care payer
Outcome	Quality-adjusted life-years (QALYs)
Time horizon	Lifetime (20 years)
Key data source	ICARIA-MM trial
Submitted results for base case	ICER = $170,541 per QALY (1.25 incremental QALYs and $213,412 incremental costs)
Key limitations	• Not all relevant comparators were included in the sponsor's base-case (i.e., cyclophosphamide, pomalidomide and dexamethasone; carfilzomib and dexamethasone). • Several issues were identified with the extrapolation of the clinical efficacy data within the submitted economic evaluation. As OS data was not mature, there was uncertainty regarding extrapolations beyond the trial period (13.9 months). Clinical experts noted that the sponsor's chosen OS and PFS curves were optimistic leading to overestimation of QALYs. • Health state utilities applied within the model lacked face validity and the inclusion of treatment-specific utilities in effect double-counted the disutility associated with adverse events. • Total drug acquisition costs of IsaPd and Pd may have been overestimated due to the sponsor's choice of the TTD parametric curve according to the clinical experts consulted on this review. • Subsequent therapies modelled in the sponsor's base case were not representative of Canadian clinical practice.
CADTH reanalysis results	• CADTH conducted a reanalysis which included: selecting the Weibull distribution for the OS of IsaPd and Pd; selecting the Gompertz distribution for PFS and TTD of IsaPd; selecting the Weibull distribution for PFS and TTD of Pd; and, revising the utility values for PFS and progressed disease health states. • Based on CADTH reanalyses, the ICER for IsaPd versus Pd is $1,555,947 per QALY gained. At a price reduction of 99.9% for isatuximab, the ICER for IsaPd versus Pd is $106,084 per QALY gained. There is no price reduction for isatuximab at which IsaPd can be considered cost-effective at a $50,000 per QALY threshold, unless there were significant price reductions for pomalidomide. At a 98% price reduction for isatuximab combined with a 50% price reduction for pomalidomide, IsaPd is cost-effective within the $50,000 per QALY threshold.

ICER = incremental cost-effectiveness ratio; IsaPd = isatuximab in combination with pomalidomide plus dexamethasone; OS = overall survival; Pd = pomalidomide plus dexamathsone; PFS = progression-free survival; QALY= quality-adjusted life-year; TTD = time-to-discontinuation.

Conclusions

Results from the ICARIA-MM trial, comparing IsaPd to Pd, was unable to demonstrate a statistical significant difference in mortality or clinically meaningful changes in HRQoL between treatment arms. Yet, the key drivers to the submitted economic model were the choice of parametric survival distributions for OS and the health-state utility values.

CADTH undertook reanalyses of the sponsor's economic model to address some of the identified limitations. CADTH's base case reanalysis included a more clinically plausible extrapolation for OS, PFS and TTD and revisions to the utility estimates. Based on CADTH reanalyses, the ICER for IsaPd versus Pd was $1,555,947 per QALY gained. With a 99.9% price reduction for isatuximab alone, the ICER decreases to $106,084 per QALY gained. Price reduction analyses suggest that, even if isatuximab was offered at zero cost, IsaPd would not be cost-effective at a $50,000 per QALY threshold as the price of pomalidomide remains high. Only upon a 98% price reduction for isatuximab combined with a 50% price reduction for pomalidomide would IsaPd be considered cost-effective within the $50,000 per QALY threshold.

The results were primarily driven by the increased acquisition cost of isatuximab and the incremental clinical benefit expected with isatuximab over the model's time horizon for IsaPd compared to Pd. A majority of the clinical benefits (61%) were observed in the extrapolation period, indicative that uncertainties in the extrapolation period remain key drivers. Many of these uncertainties could not be adequately addressed by CADTH (e.g., immature OS data, optimistic extrapolated PFS distributions that are not consistent with clinical experts' expectations). The CADTH reanalyses suggested a minor survival benefit of IsaPd relative to Pd (i.e., 0.22 additional life years). The cost-effectiveness of IsaPd compared to other relevant (and lower cost) comparator regimens such as Kd and CycloPd remains unknown at this time given the lack of evidence on its comparative effectiveness.

Based on the CADTH reanalyses, the budget impact from the introduction of isatuximab in combination with pomalidomide plus dexamethasone is expected to be $30,974,282 in Year 1, $24,653,555 in Year 2, $19,982,110 in Year 3, for a total net budget impact of $75,609,946 from the drug plan perspective.

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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