

CADTH OPTIMAL USE REPORT

Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Recommendations

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Abbreviations

AE	adverse event
BSC	best supportive care
CAR	chimeric antigen receptor
CI	confidence interval
DLBCL	diffuse large B-cell lymphoma
HTA	health technology assessment
HTERP	Health Technology Expert Review Panel
QALY	quality-adjusted life-year
r/r	relapsed or refractory
SAE	serious adverse event
WTP	willingness to pay

Summary of Recommendation

Recommendations were developed by the Health Technology Expert Review Panel (HTERP) based on evidence reviewed in a CADTH Health technology Assessment (HTA). The HTA included a review of the clinical effectiveness of axicabtagene ciloleucel,¹ an economic evaluation,² an analysis of implementation issues, a review of ethical considerations, and a review of patient perspectives and experiences.³ The HTA was additionally informed by patient group and clinician input submissions.³

HTERP deliberations and the information retrieved aimed to address the policy question: How should the provision of axicabtagene ciloleucel be structured for treating adults with eligible types of refractory or relapsed large B-cell lymphoma?

On the condition that there is a substantial reduction in price, HTERP recommends the provision of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Regarding implementation of this therapy, HTERP recommends:

- the creation of interprovincial agreements to ensure equitable access to eligible patients in all jurisdictions, including consideration of financial and logistic support for required travel and short-term relocation
- the development of clear and transparent eligibility criteria that are acceptable to patients' and clinicians' needs, based on the approved indications
- the collection of standardized outcomes data in a pan-Canadian registry of patients, which uses a defined set of outcomes and definitions to generate additional real-world evidence, for consideration in future reassessments of longer-term effectiveness, safety, and cost-effectiveness.

Technology

Axicabtagene ciloleucel (brand name Yescarta) is a second-generation chimeric antigen receptor (CAR) T-cell therapy designed to target the CD19 antigen, which is expressed on the surface of B cells, including the malignant cells involved in the aggressive B-cell non-Hodgkin's lymphomas.⁴ Health Canada approved axicabtagene ciloleucel in February 2019 for adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.⁵ It is the second CAR T-cell therapy approved in Canada.

Methods

HTERP developed recommendations on the use of axicabtagene ciloleucel based on a CADTH HTA of clinical evidence,¹ an economic evaluation,² a budget impact analysis,² an analysis of implementation considerations, and reviews of ethical issues and of patient and caregiver perspectives and experiences.³ The HTA was additionally informed by patient

group and clinician input submissions.³ HTERP members reviewed the evidence from these sources, discussed all elements of the [HTERP deliberative framework](#), and developed a consensus-based recommendation through discussion and deliberation. Additional information on the HTERP process is found on the [HTERP page](#) of the CADTH website.

Detailed Recommendations

The objective of these recommendations is to provide advice for Canadian health care decision-makers about the provision of axicabtagene ciloleucel in adults with large B-cell lymphoma.

On the condition that there is a substantial reduction in price, HTERP recommends the provision of axicabtagene ciloleucel for adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Regarding implementation of this therapy, HTERP recommends:

- the creation of interprovincial agreements to ensure equitable access to eligible patients in all jurisdictions, including consideration of financial and logistic support for required travel and short-term relocation
- the development of clear and transparent eligibility criteria that are acceptable to patients' and clinicians' needs, based on the approved indications
- the collection of standardized outcomes data in a pan-Canadian registry of patients, which uses a defined set of outcomes and definitions to generate additional real-world evidence, for consideration in future reassessments of longer-term effectiveness, safety, and cost-effectiveness.

Rationale

- HTERP was confident that there was a clinical benefit associated with axicabtagene ciloleucel, considering the findings from the CADTH clinical review and the lack of treatment options for this population.
- The clinical review reported that 71% [redacted] and 74% [redacted] of patients who were infused with axicabtagene ciloleucel achieved an objective response (either complete or partial response) within approximately six and 24 months of infusion, respectively. The objective response rate of 71% was significantly greater than the pre-specified 20% historical control ($P < 0.0001$). The overall survival at 24 months was 50.5% (95% confidence interval [CI], 40.4% to 59.7%).
- All patients in the pivotal trial experienced at least one adverse event (AE) and the incidence of serious adverse events (SAEs) was 56%. Cytokine release syndrome and cytopenias are common AEs associated with CAR T-cell therapy and require management.
- Given the lack of long-term follow-up data, the single-arm study design of the pivotal trials, and the limited number of patients in the studies, there is uncertainty in the clinical and economic evidence. Reassessment using longer-term follow-up studies and registry data will be required. Short-term studies of axicabtagene ciloleucel in the real-world setting have been conducted and presented in conference abstracts.^{6,7}
- The CADTH reanalysis found that compared with best supportive care (BSC) of palliative chemotherapy, axicabtagene ciloleucel had a 0% probability of being cost-effective at willingness-to-pay (WTP) thresholds of \$50,000 or \$100,000 per quality-adjusted life-year

(QALY). According to the CADTH reanalysis, price reductions of 60% and 83% would be required to achieve an incremental cost-utility ratio of \$100,000 and \$50,000 per QALY, respectively. These results should be interpreted with caution considering the uncertainty in the clinical evidence. The cost of axicabtagene ciloleucel may affect the ability of jurisdictions to implement the therapy.

- Models of access are likely to result in geographic inequities if not addressed by mechanisms that support out-of-province (or region) treatment, including travel. Interprovincial agreements on the appropriate eligibility criteria will be required to ensure equitable access.

Considerations

The pivotal study ZUMA-1 reported an objective response rate of 71% [REDACTED] and 74% [REDACTED] within approximately six and 24 months, respectively, and overall survival of 50.5% (95% CI, 40.4% to 59.7%) at 24 months.

All patients experienced AEs. SAEs, such as cytokine release syndrome and neurotoxicity, are common complications of treatment with axicabtagene ciloleucel and require management.

The pivotal trials were single-arm studies, in a small number of patients (N = 101) with a median (range) follow-up of 7.3 months (0.3 months to 14.0 months) for the primary analysis and 23.5 months (0.3 months to 32.4 months) for the 24-month analysis.

There is a lack of long-term follow-up data and, as such, evidentiary uncertainty for both the long-term benefits and harms of axicabtagene ciloleucel exists. There is a need to collect real-world data in registries to continue to monitor the long-term benefits and harms of this therapy. Studies of axicabtagene ciloleucel in the real-world setting have been conducted and presented in conference abstracts.^{6,7} Longer-term follow-up and data could be used with additional evidence from ongoing trials for future reassessment of the therapy.

No comparative studies are available, and future assessments are needed to allow for comparison of the clinical effectiveness and cost-effectiveness of axicabtagene ciloleucel against other CAR T-cell therapies. Should there be a difference in the efficacy or safety between CAR T-cell therapies, equity concerns may emerge.

Developing and maintaining a registry is resource intensive; therefore, it may be feasible to explore existing registries and other sources to standardize the incorporated definition and outcomes. Existing registries may have the potential to collect data for patients receiving axicabtagene ciloleucel. Standardized outcomes, including a defined set of outcomes, will be critical to ensuring the future usefulness of the registry's data in decision-making.

With the uncertainty in the clinical evidence and the lack of long-term follow-up, confidence in the cost-effectiveness results is limited. Many other factors may affect the costs of treatment, including issues with manufacturing, capacity constraints, and long-term benefits and harms — not all of which have been considered in the economic analysis. The high cost of the therapy may pose a challenge for the health care system, taking into account not only the cost of the treatment, but the additional associated costs. These associated costs include pre-treatment, post-treatment monitoring, the likelihood of additional costs due to treating AEs, and hospitalization, in addition to the costs of travel and lodging for the patients to access treatment sites. Uncertainty around these costs leads to uncertainty in the potential budget impact of implementing axicabtagene ciloleucel. Furthermore, the potential uptake of CAR T-cell products is uncertain and the overall budget impact will change if

capacity is higher or lower in the real world than predicted. Alternate payment or pricing models and risk-sharing agreements may address the limitations associated with the clinical and economic evidence.

Capacity may be affected by the number of treatment sites and may need to be increased as experience with and demand for the therapy grows; for example, by expanding either the number or volume of sites. In addition to the setting for delivery of axicabtagene ciloleucel, the availability of treatments and intensive care facilities for the treatment of possible AEs are also considerations. For example, the product monograph requires the availability of tocilizumab for the treatment of possible cytokine release syndrome following infusion with axicabtagene ciloleucel.⁸

The number and location of treatment sites may also be a factor for equitable access for patients across the country. In addition, costs, travel, and relocation to treatment sites may have social and psychological impacts. Support services for patients and caregivers may ease this burden and limit the potential issues with equity.

Other equity considerations include manufacturing and processing constraints and patient selection. There is limited information available on other possible ethical or legal considerations due to the novelty of the therapy, but uncertainty of the long-term benefits and harms, and questions about ownership of cells and consent may be raised.

Evidence

Clinical Evidence

The clinical evidence was addressed in a systematic review incorporating published evidence and information submitted by the manufacturer. The questions addressed were:

- What are the beneficial effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory large B-cell lymphoma?
- What are the harmful effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory large B-cell lymphoma?
- What are the evidence-based clinical practice guidelines for the use of axicabtagene ciloleucel for the treatment of adults with eligible types of relapsed or refractory large B-cell lymphoma?

An objective response rate was reported to be 71% [REDACTED] and 74% [REDACTED] within approximately six and 24 months of infusion in the pivotal ZUMA-1 trial, respectively.^{9,10} The objective response rate of 71% was significantly greater than the pre-specified 20% historical control that was used for the primary end point for ZUMA-1 ($P < 0.0001$). The estimated probability of overall survival was 50.5% (95% CI, 40.4% to 59.7%) at 24 months among patients in the pivotal trial.¹⁰

All patients in the pivotal trial experienced at least one AE following infusion, and 56% of patients experienced an SAE, with cytokine release syndrome and cytopenias being the most common.¹⁰

Two manufacturer-provided indirect treatment comparisons comparing axicabtagene ciloleucel [REDACTED] and with salvage chemotherapy had critical limitations, and therefore the magnitude of the potential benefits of axicabtagene versus [REDACTED] or salvage chemotherapy remain unknown.

Economic Evidence

The manufacturer-provided confidential price of axicabtagene ciloleucel is [REDACTED] per one-time treatment. The manufacturer submitted a cost-utility analysis to assess axicabtagene ciloleucel in adults with large B-cell lymphoma compared with BSC and tisagenlecleucel; CADTH reanalysis reported that axicabtagene ciloleucel was associated with an incremental cost of \$519,689 and 2.30 additional QALYs, resulting in an incremental cost-utility ratio of \$226,131 per QALY gained compared with BSC. At WTP thresholds of \$50,000 or \$100,000 per QALY, the probability that axicabtagene ciloleucel was the most likely cost-effective intervention was 0%. To be considered cost-effective at a WTP thresholds of \$100,000 or \$50,000 per QALY compared with BSC, a 60% or 83% reduction in the price of axicabtagene ciloleucel would be required, respectively.

It is estimated that [REDACTED] patients with large B-cell lymphoma will receive axicabtagene ciloleucel in the first three consecutive years of funding in Canada, assuming tisagenlecleucel (the other CAR T-cell therapy available for this indication) is also available and reimbursed. Based on CADTH's reanalysis, the three-year incremental budget impact of reimbursing axicabtagene ciloleucel is expected to be \$98.8 million under a public health care payer perspective.

Implementation Analysis

The implementation analysis was guided by two research objectives:

- Provide a detailed description of potential pathways of care for patients to receive axicabtagene ciloleucel, and the resources (e.g., health and human resources, training, organizational) needed to do so.
- Provide an overview of feasibility and capacity considerations relating to the provision of axicabtagene ciloleucel at the level of the individual patient and provider (i.e., micro level); hospital or health care organization such as health authority or region (i.e., meso level); and the provincial, territorial, and federal levels (i.e., macro level).

Structuring the provision of axicabtagene ciloleucel raises several challenges. The management of toxicities and potential for severe AEs, coupled with the need for ongoing data collection help shape potential models of delivery. The proposed model of delivery is that axicabtagene ciloleucel be delivered at manufacturer trained and qualified hematopoietic stem cell transplantation sites. The process for onboarding of sites across Canadian jurisdictions may take time, and supporting treatment across and within jurisdictions through reimbursement mechanisms and resources for patient travel (financial and logistical) may mitigate potential geographic inequalities.

As treatment sites grapple with several levels of oversight and gaining accreditation for multiple products, deciding which organizations are most suited to provide treatment sites' oversight, as well as the roles of the Foundation for the Accreditation of Cellular Therapies accreditation and of the manufacturer, involves complex considerations.

Patient selection will likely involve the selection of patients who are less stable than those in the pivotal trial supporting regulatory approval of axicabtagene ciloleucel, and bridging therapy will also likely be used in practice. Patient selection may occur across the process of receiving the therapy, and processes for allocating manufacturing slots as they become available will be needed. Uncertainty around long-term clinical effectiveness, cost-

effectiveness, and safety raises challenges for regulatory agencies and payers when making decisions, highlighting the need for long-term data collection.

Ethics Evidence

CADTH's ethics review addressed the research questions:

- What are the major ethical issues raised by the implementation of axicabtagene ciloleucel for adults with relapsed or refractory large B-cell lymphoma?
- How might these issues be addressed?

The ethics review reported that given continuing evidentiary uncertainty concerning clinical and economic evidence, from an ethics perspective, similar considerations may be required as for experimental therapies.³ This means striking a balance between the protection of vulnerable persons and the promotion of therapeutic benefit. Key ethical considerations include balancing safety and effectiveness, both short and long-term; addressing barriers to or limitations on equitable access, including geographic constraints, supply constraints, and patient selection; and considering the total cost of axicabtagene ciloleucel, including its affordability at the health system, institutional, and patient levels. These considerations underline the importance of informed choice and consent in treatment decision-making as well as recognition of psychological and emotional benefits and burdens. There may also be legal questions associated with the ownership of the genetically modified T cells. The high cost of axicabtagene ciloleucel may pose a challenge for resource allocation; therefore, opportunity costs are an important consideration. Clinical and policy implications shed light on how some of these concerns may be addressed in practice and illuminate considerations for the implementation of axicabtagene ciloleucel.

Limitations

There were no studies directly comparing axicabtagene ciloleucel with other interventions as all included studies were single-arm, open-label trials. Follow-up data past the 24-month analysis was not available at the time of the review, as studies are ongoing. Longer-term data, data from comparative studies, and additional real-world evidence are needed; therefore, this therapy may require reassessment when additional evidence is available.

Uncertainty with respect to the clinical evidence (comparative information for axicabtagene ciloleucel versus salvage chemotherapy or other CAR T-cell therapies, long-term effects, need for subsequent treatment) limits confidence in the economic results. Issues with the manufacturing and administration (including capacity constraints) of axicabtagene ciloleucel could impact the timing and effectiveness of treatment, and the expenditures associated with axicabtagene ciloleucel. Consideration of outcome-based payment models (e.g., pay for performance) may provide greater certainty around the likely cost-effectiveness.

The novelty of the therapy created limitations for the review of ethical and legal considerations and the analysis of implementation issues. There was limited published information about legal considerations. The implementation analysis and ethics review used available information on regulatory approvals, HTAs, and the implementation of axicabtagene ciloleucel in other jurisdictions. As the implementation of CAR T-cell therapies is active and ongoing, issues and practice may evolve.

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Appendix 1: The Health Technology Expert Review Panel

The Health Technology Expert Review Panel (HTERP) consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project, four expert members were appointed with expertise in hematology and oncology. The core members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. Further information regarding HTERP is available [here](#).

Health Technology Expert Review Panel Core Members

Dr. Hilary Jaeger (Chair)

Dr. Jenny Basran

Dr. Lawrence Mbugbaw

Dr. Jeremy Petch

Dr. Lynette Reid

Ms. Tonya Somerton

Dr. Jean-Eric Tarride

Expert Members

Dr. Mark Bosch

Dr. Raewyn Broady

Dr. Natasha Kekre

Dr. Maureen Trudeau

Conflict of Interest

[Conflicts of interest](#) of HTERP core members are posted on the CADTH website. Mark Bosch (Celgene, Roche), Natasha Kekre (Jazz, Jansen), and Raewyn Broady (Otsuka) have receiving travel funding for speaking engagements or lectures from industry. Natasha Kekre (Jazz, Jansen, Sanofi, Gilead) and Raewyn Broady (Jazz, Janssen, Celgene, Gilead) are members of advisory boards for industry. Maureen Trudeau receives fellow funding support (Roche, Genomic Health, Novartis, Essai, Pfizer). Natasha Kekre is involved in clinical trials with Novartis (Rituximab) and Gilead; Maureen Trudeau with Astra Zeneca, Pfizer, Astellas, Novartis, Abbvie, Roche; and Raewyn Broady with Novartis and Pharmacyclics.

[Conflict of Interest Guidelines](#) are posted on the CADTH website.

Appendix 2: Recommendations and Health Technology Assessments From Other Organizations

Organization, Country/Region	Recommendations
Regulatory Decisions	
Health Canada, Canada ^a	Approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (February 13th, 2019).
Food and Drug Administration (FDA), US ^b	Approved with Risk Evaluation and Mitigation Strategy for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (October 18, 2017).
European Medicines Agency (EMA), European Union ^c	Recommended with Risk Management Plan for the treatment of adult patients with relapsed or refractory DLBCL and PMBCL after two or more lines of systemic therapy (August 28, 2018).
Ministry of Health, Labor and Welfare, Japan ^d	Received orphan drug designation (October 3, 2018), full submission not yet made.
In-Progress HTAs for Reimbursement Decisions	
Institut national d'excellence en santé et services sociaux (INESSS), Québec	<i>In progress.</i>
National Institute for Health and Care Excellence (NICE), United Kingdom ^e	Recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory DLBCL or PMBCL in adults after two or more systemic therapies, only if the conditions in the managed access agreement are followed.
National Centre for Pharmacoeconomics (NCPE), Ireland ^f	<i>Full HTA in progress.</i>
Scottish Medicines Consortium, Scotland ^g	Not recommended for use within NHS Scotland for the treatment of adult patients with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy.

DLBCL = diffuse large B-cell lymphoma; HTA = health technology assessment; NHS = National Health Service; PMBCL = primary mediastinal large B-cell lymphoma.

^a <https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00486>.

^b <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel>.

^c <https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta>.

^d <https://lymphomanewstoday.com/2018/10/12/axicabtagene-ciloleucel-gets-japans-orphan-drug-designation-to-treat-some-non-hodgkins-lymphomas/>.

^e <https://www.nice.org.uk/guidance/TA559>.

^f <http://www.ncpe.ie/drugs/axicabtagene-ciloleucel-yescarta/>.

^g <https://www.scottishmedicines.org.uk/medicines-advice/axicabtagene-ciloleucel-yescarta-fullsubmission-smc2114/>.