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CADTH Reimbursement Recommendation

Crisantaspase Recombinant (Rylaze)

Indication: As a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma in adult and pediatric patients 1 year or older who have developed hypersensitivity to *E. coli*-derived asparaginase

Sponsor: Jazz Pharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

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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.

Summary

What Is the CADTH Reimbursement Recommendation for Rylaze?

CADTH recommends that Rylaze be reimbursed by public drug plans as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 year or older who have developed hypersensitivity to *Escherichia coli*–derived asparaginase if certain conditions are met.

Which Patients Are Eligible for Coverage?

Rylaze (crisantaspase recombinant) should only be covered to treat patients who have ALL or LBL with documented hypersensitivity to (or silent inactivation of) an *E. coli*–derived asparaginase.

What Are the Conditions for Reimbursement?

Rylaze should only be reimbursed as part of a multicomponent treatment regimen to replace pegylated *E. coli*–derived asparaginases (pegaspargase), following hypersensitivity or silent inactivation of the *E. coli*–derived asparaginase. Rylaze should be prescribed by clinicians with expertise in the management of ALL or LBL, and the cost of Rylaze should be reduced.

Why Did CADTH Make This Recommendation?

A single-arm trial showed that children and adults with ALL or LBL and hypersensitivity or silent inactivation to *E. coli*–derived asparaginase treated with 1 course (6 doses) of crisantaspase recombinant intramuscularly (IM) achieved adequate values of asparaginase activity, with adverse events (AEs) that were considered manageable and within the expected frequency of harms observed in patients with ALL or LBL. Rylaze meets an important need in the Canadian landscape due to scarcity of other options in patients with hypersensitivity or silent inactivation to asparaginase.

Based on CADTH's assessment, there is insufficient health economic evidence to determine whether Rylaze represents good value to the health care system at the public list price compared with other *Erwinia chrysanthemi (Erwinia)*-derived asparaginase (EDA) treatments. Based on public list prices, Rylaze is estimated to cost the public drug plans approximately $2.7 million over the next 3 years if the comparator EDA remains available and $26.8 million if it does not.

Summary

Additional Information

What Are ALL and LBL?

Both ALL and LBL are types of cancers of the blood and bone marrow. ALL affects a type of white blood cell called lymphocytes and LBL affects immature white blood cells (lymphoblasts). Symptoms are nonspecific and may include fatigue, pain, shortness of breath, and other symptoms. Both types of cancers are more common in children than adults and are common types of childhood cancer. Of those who receive asparaginase treatment, approximately 10% to 30% have documented hypersensitivity to asparaginase derived from *E. coli* and need other treatment options.

Unmet Needs in ALL and LBL

Asparaginase is an essential part of treating patients with ALL and LBL. As asparaginase is made from small parts of a bacteria called *E. coli*, some patients can produce antibodies against the drug, which can reduce the activity of the asparaginase and affect patients' clinical evolutions and outcomes. When this happens, doctors call it hypersensitivity (or silent inactivation when there are no symptoms); hypersensitivity prompts the need for other treatment options. There is an important need in the Canadian landscape due to issues of scarcity of other options in patients with hypersensitivity or silent inactivation to *E. coli*–derived asparaginase.

How Much Does Rylaze Cost?

Treatment with Rylaze is expected to cost approximately $24,022 per 2-week course in the pediatric and young adult population and $43,676 per 2-week course for older adults.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that crisantaspase recombinant be reimbursed as a component of a multidrug chemotherapeutic regimen for the treatment of ALL and LBL in adult and pediatric patients 1 year or older who have developed hypersensitivity to *E. coli*–derived asparaginase, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing, phase II/III, multicenter, open-label, single-arm, dose-confirmation, and pharmacokinetic study (JZP458-201) in pediatric and adult patients with ALL and LBL demonstrated that patients treated with 1 course (6 doses) of crisantaspase recombinant IM achieved adequate values of asparaginase activity. This was based on the results for the nadir serum asparaginase activity (NSAA) level assessed 48 hours following treatment (mean = 0.65 IU/mL; 95% confidence interval [CI], 0.53 to 0.77) and 72 hours following treatment (mean = 0.46 IU/mL; 95% CI, 0.34 to 0.58), both of which exceeded the predetermined threshold for NSAA level of 0.1 IU/mL. The proportion of patients with values at or above the 0.1 IU/mL threshold was higher than a 90% predetermined threshold for efficacy in 47 out of 49 patients (95.9%; 95% CI, 90.4 to 100.0) at the last 48 hours' time point, and 44 out of 49 patients (89.8%; 95% CI, 81.2 to 98.3) at the last 72 hours assessment. No other efficacy outcomes, such as overall survival, event-free survival, disease-free survival, complete clinical remission or minimal residual disease, or health-related quality of life (HRQoL) were evaluated in the study. The harms were manageable and within the expected frequency of events observed in patients with ALL or LBL in Canadian practice. Overall, pERC recognized that crisantaspase recombinant addresses a therapeutic need for additional effective options for patients with ALL or LBL with hypersensitivity to *E. coli*–derived asparaginases.

At the sponsor-submitted price for crisantaspase recombinant and the sponsor-reported price for EDA, crisantaspase recombinant was more costly than EDA on a per-cycle basis. There is insufficient evidence to justify a price premium for crisantaspase recombinant over EDA; therefore, the total drug cost of crisantaspase recombinant should not exceed the total drug cost of EDA. Crisantaspase recombinant pricing should therefore be negotiated so that it does not exceed the drug program cost for EDA.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Pediatric and adult patients who have ALL or LBL with documented hypersensitivity to an *E. coli*–derived asparaginase.	In the JZP458-201 study, patients who were hypersensitive to *E. coli*–derived asparaginases (due to at least a grade 3 allergic reaction or silent inactivation) treated with crisantaspase recombinant exhibited an increase in asparaginase activity levels that achieved an NSAA level greater than 0.1 IU/mL.	—

Reimbursement condition	Reason	Implementation guidance
2. Patients should not receive crisantaspase recombinant if: 2.1. they have a history of at least grade 3 pancreatitis.	No evidence demonstrating a benefit of crisantaspase in patients with at least grade 3 pancreatitis was identified as these patients were not enrolled in the JZP458-201 study.	—
Discontinuation		
3. Crisantaspase recombinant should be discontinued in patients who exhibit any of the following: 3.1. development of a hypersensitivity reaction or silent inactivation to crisantaspase recombinant 3.2. development of other high-grade toxicities (e.g., pancreatitis, thrombosis, and hepatotoxicity) 3.3. evidence of disease progression.	The continuous monitoring for silent inactivation, as well as disease progression, and the development of toxicities was considered a best clinical practice point based on clinical expert consensus.	To reliably assess the development of hypersensitivity or silent inactivation, NSAA levels should be monitored; however, it is acknowledged that this test might not always be available or feasible in different settings across Canada.
Prescribing		
4. Crisantaspase recombinant should be prescribed as part of a multicomponent treatment regimen in replacement of pegaspargase, following hypersensitivity to *E. coli*–derived asparaginase.	This is meant to ensure that crisantaspase recombinant is prescribed only for the appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
5. Crisantaspase recombinant should be prescribed by clinicians with expertise in the management of ALL or LBL.	This is meant to ensure that crisantaspase recombinant is prescribed only for the appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. Crisantaspase recombinant should be negotiated so that it does not exceed the per-cycle drug program cost of treatment with the least costly EDA reimbursed for the treatment of ALL or LBL.	Uncertainty in the indirect evidence precluded pERC from drawing conclusions about the clinical benefit of crisantaspase recombinant compared to EDA. As such, there is insufficient evidence to justify a per-cycle cost premium for crisantaspase recombinant over the least expensive EDA reimbursed for patients with ALL or LBL who are hypersensitive to *E. coli*–derived asparaginase.	—

ALL = acute lymphoblastic leukemia; EDA = *Erwinia*-derived asparaginase; LBL = lymphoblastic lymphoma; NSAA = nadir serum asparaginase activity; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.

Discussion Points

- The Provincial Advisory Group (PAG) requested a reconsideration of the initial draft recommendation to reimburse crisantaspase recombinant as a component of a multidrug chemotherapeutic regimen for the treatment of ALL and LBL in adult and pediatric patients 1 year or older who have developed hypersensitivity to *E. coli*–derived asparaginase. Specifically, PAG noted that crisantaspase recombinant may also benefit patients who have relapsed or refractory ALL or LBL. pERC discussed this issue identified by PAG in its request for reconsideration.
- pERC discussed the need for the availability of other therapies in patients with ALL and LBL with hypersensitivity to *E. coli*–derived asparaginases. pERC acknowledged that EDA may be used in these cases; however, EDA is not currently marketed in Canada, and was available only through exceptional importation and sale. The sponsor indicated that global shortages make the supply of EDA burdensome; however, as part of the request for reconsideration, PAG noted that the supply of EDA at time of PAG's feedback showed no drug shortage of EDA. Given the potential for challenges accessing EDA in Canada, pERC concluded that there is a need for additional treatment options.
- Because there was uncertainty with the clinical evidence given the single-arm study design, pERC deliberated on crisantaspase recombinant considering the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. pERC noted that the efficacy observed in the trial is based on a surrogate but objective end point (NSAA levels), and that patients with ALL and LBL who suffer from hypersensitivity to *E. coli*–derived asparaginases (an important component in their treatment regimens) have an absence of available effective alternative therapies. Therefore, the committee concluded that the available evidence was sufficient to suggest that crisantaspase recombinant has the potential to be used as a component of a multidrug chemotherapy regimen in these patients.
- During the reconsideration discussion, pERC also discussed the significant unmet need for patients who have relapsed or refractory ALL or LBL. Although patients with relapsed ALL or LBL were excluded from the JZP458-201 study, input from the clinical experts consulted by CADTH and feedback from clinician groups highlighted that in practice, pediatric protocols for patients with relapsed or refractory ALL or LBL use asparaginase drugs, including for those who develop a pegaspargase allergy in relapsed or refractory therapy. pERC also noted that it would not be possible to specifically study the safety and efficacy of crisantaspase recombinant in this small patient population of pediatric patients with relapsed or refractory disease. Furthermore, there are even fewer adult patients with relapsed or refractory disease who require asparaginase as there are alternative treatment options for adult patients. Overall, pERC agreed that if patients are otherwise eligible and have developed hypersensitivity to *E. coli*–derived asparaginase, then they should be eligible for crisantaspase recombinant.
- pERC considered the indirect treatment comparison (ITC) submitted by the sponsor, which was a naive comparison to evaluate the relative clinical efficacy of crisantaspase recombinant versus EDA for the treatment of ALL or LBL in patients with hypersensitivity to *E. coli*–derived asparaginase. The

naive ITC showed that a high proportion of patients in both treatment groups reached the threshold for adequate asparaginase activity and exhibited a similar safety profile with both treatments; however, the results are highly uncertain due to risk of bias, confounding, and imprecision due to the low number of patients and wide CIs.

- pERC discussed the importance of therapeutic drug monitoring (TDM) in the management of patients treated with asparaginase as a reliable assessment of asparaginase efficacy. Tracking of asparaginase activity (NSAA levels) is used to initiate and monitor response throughout treatment regimens, as well as to distinguish between hypersensitivity due to an allergic reaction (or silent inactivation) and other types of asparaginase reactions that do not result in inactivation. However, pERC acknowledged that routine TDM might not always be available or feasible in different settings across Canada, which results in inconsistent use in clinical practice.
- pERC discussed that the toxicity profile of crisantaspase recombinant based on the results from the JZP458-201 study may not be generalizable to older patients, who may be at a higher risk of AEs, since patients older than 25 years were not represented in the pivotal trial.
- When considering the request for reconsideration, pERC discussed that, given the rarity of the condition and context of hypersensitivity to pegaspargase, there are few patients with ALL or LBL who develop hypersensitivity to *E. coli*–derived asparaginase. Furthermore, the population of patients who subsequently have relapsed or refractory disease who then receive re-treatment with pegaspargase and develop hypersensitivity would be exceedingly small. The sponsor's cost-utility analysis estimated that 5% of pediatric patients would relapse within 5 years, and the clinical expert consulted by CADTH indicated that the number of adult patients with relapsed or refractory ALL or LBL who would require crisantaspase recombinant is also very small. As such, pERC did not anticipate that this would have a meaningful impact on economic or budgetary considerations.

Background

ALL and LBL are hematological malignancies characterized by a rapidly progressing transformation and proliferation of lymphoid blasts in the bone marrow, peripheral blood, and other organs. These conditions are considered intersecting clinical presentations of the same disorder with likely multifactorial risks. Approximately 80% to 85% of ALL cases are B-cell phenotypes in children, as are close to 75% in adults. ALL and LBL have bimodal age distributions, with a first peak in childhood (3 out of 4 cases occur in children aged younger than 6 years), and a second peak in adults aged older than 60 years. In Canada, the incidence of ALL and LBL is 1.3 cases per 100,000 persons of all ages. ALL and LBL has an important impact on the quality of life of patients and caregivers; it also has emotional, financial, and developmental effects. Prognosis is generally poor in adults (with a 5-year survival rate of 40% to 70%) with older age associated with worse survival, while children and adolescents have better prognosis (with remission in 98% of patients, a 5-year survival rate of higher than 90%, and long-term event-free survival of 85%).

Asparaginase (L-asparaginase) is an essential part of the treatment of ALL and LBL in the induction, consolidation, and intensification phases. It consists of bacterial enzymes derived from either *E. coli* or

Erwinia. Given the nonhuman origin of *E. coli*–derived asparaginases, patients can react by producing antibodies to the drug, which can substantially reduce the activity of asparaginase and affect patients' clinical evolutions and outcomes. Also is the potential for silent inactivation – the formation of neutralizing antibodies and reduced asparaginase activity in the absence of clinical hypersensitivity symptoms. EDA is commonly used as an alternative for patients with hypersensitivity or allergic reactions to *E. coli*–derived asparaginase. However, this product was cancelled in Canada postmarket in 2021 and is only available via Health Canada Exceptional Importation with a Tier 3 drug shortage designation.

Crisantaspase recombinant has been approved by Health Canada as a component of a multidrug chemotherapeutic regimen for the treatment of ALL and LBL in adult and pediatric patients 1 year or older who have developed hypersensitivity to *E. coli*–derived asparaginase. Crisantaspase recombinant is expressed in Pseudomonas fluorescens with an identical amino acid sequence to native EDA. It is available as a solution for IM injection containing 10 mg/0.5 mL (20 mg/mL) and the dosage recommended in the product monograph is 25 mg/m^2 on Monday and Wednesday, and 50 mg/m^2 on Friday, for a total of 6 doses to replace each planned dose of pegaspargase.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 single-arm study in adult and pediatric patients with ALL or LBL
- patient perspectives gathered by 1 patient group, the Leukemia & Lymphoma Society of Canada (LLSC)
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with ALL and LBL
- input from 2 clinician groups, including the Hematology Cancer Drug Advisory Committee from Ontario Health-Cancer Care and the Pediatric Oncology Group of Ontario (POGO)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the Request for Reconsideration (described in the following).

Stakeholder Perspectives

Patient Input

One patient group, the LLSC, supplied patient group input for this review. The LLSC gathered input from 40 respondents (1 of whom had experience with crisantaspase recombinant) via an online survey distributed in English and French through social media networks, as well as by email.

Interviewed patients often reported fatigue and/or weakness (68% of the total respondents) and loss of appetite or weight loss (45% of the respondents) as issues having a significant impact on quality of life. Disease symptoms had a significant impact on the respondents' ability to work, exercise, and continue daily

activities (64% of respondents). Also, significant impacts on stress and anxiety and problems concentrating due to disease symptoms were reported by 68% and 64% of the respondents, respectively.

In open-ended responses, side effects of treatments for their condition were highlighted as important, with some respondents providing comments such as, "the chemotherapy protocol is long and extremely tiring" or "very difficult protocol of chemotherapy." A total of 8 patients reported being in treatment for 4 or more years, and 6 mentioned having had more than 5 total lines of treatment. When starting new treatments, patients considered the least amount of travel needed, improved quality of life, and insurance coverage as crucial factors for decisions. Reduced side effects were also often mentioned when respondents were asked what improvements they would like to see for any new treatment for ALL.

The 1 respondent who reported experience with crisantaspase recombinant described manageable side effects and indicated that the disease responded completely to the treatment. The patient mentioned allergic reactions to other previously used chemotherapies and expressed a preference for the treatment to be in IV form rather than IM injection.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH agreed that the treatment goals of asparaginase as part of a multicomponent chemotherapeutic regimen in patients with ALL and LBL include maximizing cure rates while minimizing short- and long-term side effects, improving HRQoL, and reducing caregiver burden. Pegaspargase is the mainstay asparaginase treatment option, though clinically evident hypersensitivity reactions to *E. coli*–derived asparaginase occur in 10% to 15% of patients, and a smaller percentage of patients develop silent inactivation. The clinical experts noted that, given the established importance of asparaginase therapy in the treatment of ALL and LBL, discontinuation of asparaginase therapy would likely lead to inferior survival outcomes and switching to EDA would be the next best option. The global supply of EDA has been limited due to manufacturing difficulties, highlighting the need for a more reliable supply of EDA.

In regard to place in therapy, the clinical experts indicated that crisantaspase recombinant should be used as a component of a multidrug regimen for the treatment of ALL and LBL in patients who have developed a documented hypersensitivity reaction or silent inactivation to *E. coli*–derived asparaginase. The experts also noted that the potential advantage of crisantaspase recombinant is having a better and more reliable supply chain.

The clinical experts noted that the patients best suited for treatment with crisantaspase are those who experience a true antibody-mediated hypersensitivity reaction or silent inactivation, as documented by a decrease in NSAA. Measurement of NSAA is required to detect patients with silent inactivation of asparaginase activity; therefore, the clinical experts believed that measurement of NSAA should be considered a standard of care in patients receiving asparaginase products and should be made widely available in Canada.

For assessing response to treatment of ALL and LBL, the outcomes used to determine whether a patient is responding include post hoc evaluations such as event-free survival, disease-free survival, and overall survival. For assessing response to treatment, TDM should be performed if available. According to the clinical experts, the potential reasons for discontinuing treatment with crisantaspase include development of hypersensitivity reaction or silent inactivation to the drug, development of other types of toxicities (e.g., pancreatitis, thrombosis, and hepatotoxicity), evidence of disease relapse, or change in treatment strategy that no longer requires asparaginase therapy (e.g., allogeneic bone marrow transplant).

The clinical experts indicated that any asparaginase preparation (including crisantaspase) can acutely result in anaphylaxis or other serious allergic reactions; hence, for safety reasons, these drugs should only be given in the inpatient or outpatient hospital setting with immediate availability of suitably trained personnel who can acutely assess the severity of AEs and provide emergency interventions as required.

Clinician Group Input

Two clinician groups provided input for this CADTH submission. The Hematology Cancer Drug Advisory Committee of Ontario Health-Cancer Care Ontario and the Pediatric Oncology Group of Ontario. Both groups obtained advice by interviewing clinical experts in the field of cancer, with a focus for this CADTH submission on ALL and LBL in both adults and children.

The information provided by both groups was aligned with the input from the clinical experts consulted by CADTH in relation to the importance of asparaginase treatment as part of a multidrug chemotherapy for patients with ALL and LBL and on the need for a replacement in the presence of overt allergy or silent inactivation that occurs in up to 25% of patients (according to input from the pediatric group). The groups mention that *Erwinia*-based treatments are currently the only available choice for this purpose, but there is supply shortage and unavailability for patients and clinicians in Canada. The clinician groups agreed that this situation could lead to incomplete treatment schedules and poorer patient outcomes. The clinician groups and the clinician experts also agreed that the patients best suited for treatment with crisantaspase recombinant are those with overt allergy and silent inactivation. The clinician groups also concurred that patients should be able to access the drug and that NSAA testing should be available to monitor response to treatment for anyone receiving asparaginase products.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Erwinase/*Erwinia* L-asparaginase is available in most jurisdictions for this indication. Erwinase is currently imported from the UK through Health Canada Exceptional Importation with a Tier 3 drug shortage designation and	This was a comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
is currently being reevaluated by Health Canada after post market cancellation in 2021.	
Considerations for initiation of therapy	
Patients were eligible for this trial if they experienced a grade 3 or greater allergic reaction to a pegylated *E. coli*–derived asparaginase. Can results be applied to patients with a lesser grade reaction?	The clinical experts indicated that the treatment of patients with a lesser grade allergic reaction depends on their asparaginase activity levels. To determine the asparaginase activity levels, a test (NSAA) must be run. The clinical experts indicated that access to the test required to determine the levels is an issue as it is not universally funded. pERC agreed with the clinical experts and acknowledged that treatment should not be restricted if testing is not readily available.
Considerations for prescribing of therapy	
Crisantaspase recombinant is administered 3 times per week at a dosage of 25mg/m^2 IM on Mondays and Wednesdays and 50mg/m^2 IM on Fridays.	This was a comment from the drug programs to inform pERC deliberations.
Care provision issues	
EDA (Erwinase) is under Health Canada review. If supply becomes available, under what circumstances would crisantaspase recombinant (Rylaze) be preferred over EDA (and vice versa)?	The clinical experts indicated that preference for crisantaspase recombinant over EDA (and vice versa) is largely dependent on the availability of either product. If supply is not an issue, the clinical experts could not comment on which treatment is better or preferred based on the available evidence. The clinical experts also indicated that if supply is not an issue, it would be challenging to provide a rationale for the use of crisantaspase recombinant over EDA if crisantaspase recombinant is more expensive. They indicated that this may result in off-label use of crisantaspase recombinant (25 mg/m^2 on Friday rather than 50 mg/m^2). pERC notes that, as the safety profiles seem to be similar, price will play an important role in this decision if there is no evidence of superiority of 1 over the other.

EDA = *Erwinia*-derived asparaginase; IM = intramuscular; NSAA = nadir serum asparaginase activity; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Description of Studies

One study was included in this review — an ongoing, open-label, single-arm, multicenter, dose-confirmation, and pharmacokinetic trial of crisantaspase recombinant in pediatric and adult patients with ALL or LBL who have hypersensitivity (an allergic reaction and/or silent inactivation) to *E. coli*–derived asparaginases. The study was designed to assess the efficacy and harms of crisantaspase recombinant. The main efficacy end point was measured with the asparaginase activity (with NSAA levels ≥ 0.1 IU/mL as a meaningful threshold) assessed at 48 hours and 72 hours. The study was initiated on December 27, 2019, and the data cut-off for the available analysis was July 19, 2021. In this study, 6 doses of crisantaspase recombinant

are substituted for each dose of a long-acting *E. coli*–derived asparaginase. Doses were administered on a Monday, Wednesday, and Friday schedule for 2 consecutive weeks; 2 consecutive weeks of treatment with crisantaspase recombinant is defined as 1 course. The focus of this review was on cohort 1c of the study, which included 51 patients following a dosing schedule of 25 mg/m^2 on Mondays and Wednesdays and 50 mg/m^2 on Fridays, which is the approved Health Canada indication. The population was mostly made up of young people (range = 3 to 25 years of age) and most (46 of 51; 90%) were diagnosed with ALL. Grade 3 or higher allergic reaction to previous *E. coli*–derived asparaginase occurred in 44 of 51 patients, with 1 silent inactivation, and 6 allergic reactions with inactivation.

Efficacy Results

The outcomes set in the protocol of this CADTH review were efficacy outcomes such as overall survival, event-free survival, disease-free survival, complete clinical remission and minimal residual disease, HRQoL, and serum asparaginase activity (i.e., serum NSAA levels). Of these end points, only NSAA and harms were available from the pivotal trial. The serum asparaginase activity levels are a surrogate marker for asparagine depletion, and an NSAA level 0.1 IU/mL or more is the most widely accepted threshold to demonstrate adequate asparagine depletion in clinical practice.

Overall, values of the mean and median NSAA showed that the dosage of cohort 1c (25 mg/m^2 Monday and Wednesday, and 50 mg/m^2 Friday) reached values above the 0.1 IU/mL threshold for both the last 48 hours (mean = 0.65 IU/mL; 95% CI, 0.53 to 0.77) and the last 72 hours (mean = 0.46 IU/mL; 95% CI, 0.34 to 0.58) assessments. When measuring the number and proportion of patients with values at or above the 0.1 IU/mL threshold, this was achieved in 47 out of 49 patients analyzed (95.9%; 95% CI, 90.4 to 100.0) at the last 48 hours time point (achieving the sponsor's threshold for efficacy of 90%) and 44 of 49 patients (89.8%; 95% CI, 81.2 to 98.3) at the last 72 hours assessment. Both proportions were considered clinically relevant by the clinical experts consulted by CADTH.

Harms Results

Harms outcomes included mortality, AEs, serious adverse events (SAEs), and withdrawals due to AEs. Notable harms comprised thrombosis, pancreatitis, hypersensitivity reaction, hepatotoxicity, and hypertriglyceridemia (in adults). The safety outcomes were assessed in the safety analysis set. As of the data cut-off date of July 19, 2021, a total of 167 patients (33 in cohort 1a [IM 25 mg/m^2 Monday, Wednesday, and Friday], 83 in cohort 1b [IM 37.5 mg/m^2 Monday, Wednesday, and Friday], and 51 in cohort 1c [25 mg/m^2 Monday and Wednesday, and 50 mg/m^2 Friday]) were included in the safety analysis set for part A (IM) of the study. The focus on this report is the cohort 1c as this group includes the dosage approved by Health Canada.

For cohort 1c, a total of 49 of 51 (96.1%) patients reported at least 1 AE. In all patients in the IM cohort, 164 of 167 (98.2%) presented at least 1 AE. The most frequent AEs in cohort 1c, up to the latest cut-off date, have been anemia (52.9%; 27 out of 51), decreased platelet count (45.1%; 23 out of 51), decreased neutrophil count (47.1%; 24 out of 51), and vomiting (33.3%; 17 out of 51). In the whole IM cohort, these numbers were similar, with anemia (53.3%; 89 out of 167), decreased platelet count (43.7%; 73 out of

167), decreased neutrophil count (43.1%; 72 out of 167), and vomiting (42.5%; 71 out of 167). These and other AEs, such as pyrexia, fatigue, febrile neutropenia, decreased white blood cell count, stomatitis, and increased alanine transaminase (ALT), were considered by the clinical experts consulted by CADTH to be of common occurrence in all patients with ALL and LBL treated with asparaginase as part of a multicomponent chemotherapy regimen. The clinical experts indicated that many of the AEs likely resulted from the chemotherapy regimen.

A total of 30 of 51 (58.8%) of those included in cohort 1c experienced at least 1 SAE. The most common SAEs (in at least 5% of patients) were febrile neutropenia (25.5%), pyrexia (11.8%), investigations (11.8%), sepsis (9.8%), pancreatitis (any kind = 5.9%; acute = 2.0%), and renal and urinary disorders (5.9%). All other SAEs were reported in less than 5% of patients. In the total IM-treated cohort (part A of the study), 107 of 167 patients (64.1%) experienced at least 1 SAE at the time of the data cut-off (July 19, 2021). The most common AEs (occurring in ≥ 5% of patients) were febrile neutropenia, anemia, gastrointestinal disorders, pyrexia, stomatitis, and sepsis. As with AEs, these were considered by the clinical experts to be within the expected frequency and part of the ALL and LBL therapy. No deaths occurred in cohort 1c, and a total of 3 of 167 patients (1.8%) had a fatal event, with 1 in cohort 1a and 2 in cohort 1b.

Among the notable harms, allergic reactions (hypersensitivity and anaphylaxis) occurred in 18 (35.3%) patients in cohort 1c. The most frequently reported events related to allergic reactions in this cohort included rash (7.8%; 4 out of 51), dermatitis (7.8%; 4 out of 51); and allergic transfusion reaction (7.8%; 4 out of 51). As of the data cut-off date (July 19, 2021), 6 of 51 patients in cohort 1c (11.8%) had pancreatitis. Thrombosis occurred in only 1 of the 51 patients included in cohort 1c. Hepatic toxicity was observed in 13 of 51 patients (25.5%) in cohort 1c and all cases consisted of elevated levels of ALT, aspartate aminotransferase, and bilirubin. Hypertriglyceridemia occurred in 6 of the 51 patients (11.8%) in cohort 1c.

Critical Appraisal

The main limitation of the included study is the single-arm (noncomparative) design. As a result of the lack of comparator group and no control for confounding, the outcomes cannot be definitively attributed to the administration of crisantaspase recombinant. It is recognized that supply shortages of the main comparator (EDA) may have rendered a randomized comparison infeasible. The selection criteria appear reasonable, and the risk of selection bias is probably low. No formal hypothesis testing was performed to assess the effects estimates from this study. Bias in measurement of the outcome is not suspected because efficacy measurements, such as NSAA levels, were collected objectively. Overreporting of known harms is possible, but the extent to which this may have occurred is not possible to quantify. An evaluation of the comparative efficacy of crisantaspase recombinant and EDA is limited by the shortcomings of this study. Noting these limitations and the uncertainty in the information provided, crisantaspase recombinant may still behave similarly to the drug it aims to replace (*E. coli*–derived asparaginase) in the multicomponent chemotherapy regimen for patients with ALL and LBL; however, this was not tested. The efficacy analysis was performed on the efficacy analysis set, which included all patients who received at least 1 dose of the study drug and had at least one 48-hour or 72-hour NSAA assessment in course 1. Only 1 assigned patient is missing from this analysis set (compared to the enrolled set); therefore, there are no concerns for bias related to this decision.

The pivotal study can only highlight that crisantaspase recombinant is associated with measurable asparaginase activity with an NSAA level above a threshold of 0.1 IU/mL, previously set as an important limit of clinical importance. This end point, however, is used and should be interpreted as a surrogate for important clinical outcomes.

Indirect Comparisons

Description of Studies

One sponsor-submitted ITC comparing crisantaspase recombinant and EDA was included. The body of evidence in this ITC consisted of 2 single-arm studies, 1 of crisantaspase recombinant and the other of EDA. Since a network meta-analysis or other population-adjusted ITCs were unfeasible, the analysis was achieved through a naive comparison of the single treatment arm from each study and calculation of odds ratios (ORs) for the effect estimates. The populations and outcome definitions were overall similar between the studies for assessing a comparison. There were some differences in the inclusion and exclusion criteria, and patients in the crisantaspase recombinant trial were slightly older and were more recently diagnosed compared to the EDA trial. The EDA trial included only patients with ALL, and no patients with LBL. The outcomes evaluated are the proportion of patients reaching an NSAA level of 0.1 IU/mL or higher, and harms. The ITC presented effect estimates with uncertainty due to risk of bias, confounding (single-arm studies without adjustments to balance unobserved prognostic factors or effect modifiers), and imprecision. Hence, any difference of effects between crisantaspase recombinant and EDA is difficult to ascertain.

Efficacy Results

Among the efficacy outcomes of interest for this review (overall survival, event-free survival, disease-free survival, complete clinical remission and minimal residual disease, HRQoL) only the NSAA levels, measured as a proportion of patients reaching an NSAA level above 0.1 IU/mL was evaluated, no long-term evaluation of any outcome is available at this point.

In the crisantaspase recombinant study, 47 of 49 (95.9%) patients reached an NSAA level of 0.1 IU/mL or greater in the last 48-hour assessment time, while 38 of 41 (92.7%) of patients in the EDA study reached this threshold (OR = 1.86; 95% CI, 0.29 to 11.68). Similarly, 44 of 49 (89.8%) patients in the crisantaspase recombinant study reached an NSAA level of 0.1 IU/mL or more in the last 72-hour assessment time while 38 of 43 (88.4%) patients in the EDA study reached this threshold (OR = 1.16; 95% CI, 0.31 to 4.31).

No other efficacy end points were evaluated in the study.

Harms Results

The sponsor-submitted ITC assessed specific outcomes of interest but no overall AEs. Also, it included patient discontinuations as an outcome, which was defined by the number of patients who had completed all remaining courses. Overall, no evidence of a difference was observed in the proportions of patients with increased ALT levels (grade 3 or 4), thrombosis, or hyperglycemia, as well as trial completion between the EDA and crisantaspase recombinant groups.

An increased ALT level (grade 3 or 4) was observed in 7.8% of patients in the crisantaspase recombinant trial versus 5% of patients in the EDA trial. A total of 6 patients (11.8%) developed pancreatitis in the crisantaspase recombinant trial, in comparison to 1 patient in the EDA trial (1.8%). [redacted] Of the 8 patients who developed drug hypersensitivity in the EDA trial, it was reported that 5 (9% of the total population) developed grade 3 or 4 hypersensitivity. [redacted] A total of 7 patients developed hyperglycemia in the EDA trial (12%), whereas 6 patients (11.8%) in the crisantaspase recombinant trial developed hyperglycemia. Completed courses of planned asparaginase therapy were achieved by 55 (80%) patients in the EDA trial, while in cohort 1c of the crisantaspase recombinant trial (still ongoing at the time of this analysis) it was assumed that a total of 42 patients (82.4%) had completed their eligible courses to date.

Critical Appraisal

The main limitation of the ITC is mostly due to the characteristics of the individual studies conforming the body of evidence. The ITC is achieved through a naive comparison of each treatment arm from each study, as performing a network meta-analysis or a population-adjusted ITC was not feasible due to the small sample size of each single-arm trial. The baseline demographics and study characteristics reported were overall similar, but due to the nature of the comparison, there is no certainty on the balance of unobserved prognostic factors or effect modifiers; hence, any difference of effects between crisantaspase recombinant and EDA is difficult to ascertain. There is large imprecision when estimating the OR for both comparisons due to a large number of events in a small number of patients. The same limitation applies when evaluating harms. Overall, the crude numbers of AEs in both included studies were similar, and within the expected incidence according to the clinical experts consulted by CADTH. The incidence of AEs is likely to be affected by the background chemotherapy regimens, which may have differed across trials as a result of the time period during which they were undertaken. Additionally, there were some differences in the definitions used for AEs across the trials, and differences in inclusion criteria may have biased the naive comparison of AEs.

There were no major concerns in terms of the external validity, aside from those previously noted for the trial of crisantaspase recombinant. Overall, the populations, interventions, and outcomes assessed in the ITC were considered by the clinical experts consulted by CADTH to be generalizable to the Canadian population, as well as to clinical practice, for the specific question and indication assessed in this review. Some differences were noticed, such as in the condition included (for instance, there were no patients with LBL in the EDA study) and the lack of adult patients (≥ 25 years old) in both studies.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis, Markov model
Target populations	Adult and pediatric patients 1 year and older with ALL or LBL who have developed hypersensitivity (i.e., an allergic reaction) to an *E. coli*–derived asparaginase. The population was split into 2 subgroups based on age: children and young adults (younger than 25 years); and adult patients (aged 25 years or older).
Treatment	Crisantaspase recombinant
Dose regimen	25 mg/m^2 of BSA on Monday and Wednesday and 50 mg/m^2 on Friday for a total of 6 doses to replace each planned dose of pegaspargase
Submitted price	10 mg/0.5 mL vial: $1,091.91
Treatment cost	$24,022 per 2-week course ($96,088 for 4 courses) in the pediatric and young adult population (mean BSA = 0.97 m^2) $43,676 per 2-week course ($174,706 for 4 courses) in adults 25 years or older (mean BSA = 1.95 m^2).
Comparators	Base case: EDA Scenario: BSC, defined as an unspecified chemotherapy regimen without an asparaginase component
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (100 years)
Key data source	The JZP458-201 trial, a sponsor-conducted ITC, previous cost-effectiveness analyses
Key limitations	• The comparative safety and efficacy of crisantaspase recombinant and EDA are highly uncertain due to the reliance on a surrogate primary outcome and the absence of direct or nonnaive indirect evidence. • There is a lack of direct or indirect evidence comparing crisantaspase recombinant to BSC, forcing assumptions regarding relative clinical efficacy based on weighted mean EFS results from historical trials of pegaspargase compared to BSC regimens. • Mortality is poorly modelled and highly uncertain, particularly in the older adult population, where OS was assumed to equal EFS, and patients aged older than 25 years were thus not assumed to experience remission of ALL or LBL. • The treatment duration of 4 asparaginase cycles assumed in the model may not be reflective of average use in Canada. • Utility values are likely overestimated, particularly in the older adult population, who were assumed to have the same quality of life as the general population after year 2, despite very high mortality. • The list price of EDA is uncertain given pending changes in its regulatory status and availability.
CADTH reanalysis results	• CADTH was unable to derive a base-case reanalysis due to the lack of comparative clinical evidence and the structural limitations of the sponsor's submitted pharmacoeconomic model. Instead, CADTH made minor corrections to the sponsor's base case and then conducted a series of exploratory scenario analyses establishing the sponsor's results as sensitive to changes in the duration of asparaginase therapy, the mortality decrement applied to patients who could not access and/or tolerate second-line asparaginase, the relative efficacy of EDA compared to crisantaspase recombinant, and the decreased

Component	Description
	utility values implemented for older adult patients in years 3 and beyond. • At the submitted price, a price reduction of 25% would be required for the cost of crisantaspase recombinant to be equivalent to the assumed price of EDA, due to differences in their relative dosing schedules. Given the high degree of uncertainty around the effectiveness of crisantaspase recombinant compared to both EDA and BSC, a price reduction greater than 25% may be required.

ALL = acute lymphoblastic leukemia; BSA = body surface area; BSC = best supportive care; EDA = *Erwinia*-derived asparaginase; EFS = event-free survival; ITC = indirect treatment comparison; LBL = lymphoblastic lymphoma; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the Non-Insured Health Benefits population was double counted, treatment duration with asparaginase may not reflect current Canadian practice, asparaginase might not be given to adult patients with Philadelphia chromosome–positive ALL, and the future availability of EDA is uncertain.

CADTH corrected the Non-Insured Health Benefits and provincial populations to avoid double counting. CADTH also conducted a series of scenario analyses exploring the impact of adjusting treatment duration, assuming adults with ALL who were Philadelphia chromosome positive would not receive asparaginase, assuming the future supply of EDA will only be sufficient for half of patients in Canada who would otherwise be eligible, and introducing a 25% price reduction for crisantaspase recombinant.

The corrected sponsor's analyses suggest that:

- Should EDA be available, the reimbursement of crisantaspase recombinant for the treatment of ALL and LBL in patients with a grade 3 or higher hypersensitivity reaction would be $772,040 in year 1, $908,555 in year 2, and $1,048,073 in year 3, for a 3-year incremental cost of $2,728,668.
- Should EDA not be available, the reimbursement of crisantaspase recombinant for the treatment of ALL and LBL in patients with a grade 3 or higher hypersensitivity reaction would be $8,822,874 in year 1, $8,928,195 in year 2, and $9,033,516 in year 3, for a 3-year incremental cost of $26,784,584.

The estimated budget impact of reimbursing crisantaspase recombinant is highly sensitive to assumptions around the duration of asparaginase treatment and the future availability and reimbursement of EDA.

Request for Reconsideration

PAG filed a request for reconsideration for the draft recommendation for crisantaspase recombinant as a component of a multidrug chemotherapeutic regimen for the treatment of ALL and LBL in adult and pediatric patients 1 year or older who have developed hypersensitivity to *E. coli*–derived asparaginase. In its request, PAG identified the following issue that was aligned with feedback received from the clinician group:

- Patients with relapsed or refractory ALL or LBL were excluded from the JZP458-201 study. However, if a patient with relapsed or refractory ALL has a documented hypersensitivity (or silent inactivation) to an *E. coli*–based asparaginase, then they would not have access to crisantaspase recombinant in the relapsed or refractory setting. There are protocols for relapsed or refractory ALL or LBL that

incorporate asparaginase products. If a patient has hypersensitivity or silent inactivation to an *E. coli* asparaginase product, they would not be able to access crisantaspase based on this initial recommendation.

In the meeting to discuss the sponsor's request for reconsideration, pERC considered information from the initial submission relating to the issue identified by PAG, as well as feedback on the draft recommendation from:

- the sponsor
- 2 clinical specialists with expertise in the diagnosis and management of patients with ALL and LBL
- 1 clinician group, the Pediatric Oncology Group of Ontario
- 1 patient group, the LLSC.

All stakeholder feedback received in response to the draft recommendation from clinician groups, patient groups, and the sponsor is available on the CADTH website.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Initial Meeting Date: January 11, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: April 12, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None