CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Reimburse with Conditions

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Single Technology

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that crisantaspase recombinant be reimbursed 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 *E. coli*-derived asparaginase, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing, phase 2/3, 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% 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 pre-determined 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 above a pre-determined threshold for efficacy of 90%, achieved in 47 out of 49 patients (95.9% [95% CI, 90.4 to 100.0]) at the last 48 hours timepoint and 44 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/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 or silent inactivation of *E. coli*-derived asparaginases.

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

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 (or silent inactivation of) 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 a NSAA level greater than 0.1 IU/mL.	–
2. Patients should not receive crisantaspase recombinant if: 2.1. they have relapsed ALL or LBL 2.2. they have a history of at least Grade 3 pancreatitis	Patients with relapsed ALL or LBL with a history of at least grade 3 pancreatitis were excluded from the JZP458-201 study and therefore, the effects of crisantaspase recombinant on this group is uncertain.	–
Discontinuation		
3. Crisantaspase recombinant should be discontinued in patients who exhibit any of the following: 3.1. development of 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 multi-component treatment regimen in replacement of PEG-asparaginase, following hypersensitivity or silent inactivation of the *E. coli*-derived asparaginase.	To ensure that crisantaspase recombinant is prescribed only for appropriate patients and 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.	To ensure that crisantaspase recombinant is prescribed only for appropriate patients and 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	Uncertainty in the indirect evidence precluded pERC from drawing conclusions about the clinical benefit of crisantaspase recombinant compared to Erwinia-derived	—

Reimbursement condition	Reason	Implementation guidance
with the least costly *Erwinia*-derived asparaginase reimbursed for the treatment of ALL or LBL.	asparaginase. As such, there is insufficient evidence to justify a per-cycle cost premium for crisantaspase recombinant over the least expensive *Erwinia*-derived asparaginase reimbursed for patients with ALL or LBL who are hypersensitive to *E. coli*-derived asparaginase.	

ALL = acute lymphoblastic leukemia; LBL = lymphoblastic lymphoma; NSAA = nadir serum asparaginase activity; SAA = serum asparaginase activity.

Discussion Points

- pERC discussed the needs for the availability of other therapies in patients with ALL and LBL with hypersensitivity or silent inactivation to E. coli-derived asparaginases. pERC acknowledged that *Erwinia*-derived asparaginase (EDA) may be used in these cases; however, EDA is not currently marketed in Canada, and was available only through exceptional importation and sale. Furthermore, global shortages make the supply of EDA burdensome. Given the 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 endpoint (NSAA levels), and that patients with ALL and LBL who suffer from hypersensitivity to or silent inactivation of 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 multi-agent chemotherapy regimen in these patients.
- pERC considered the indirect treatment comparison (ITC) submitted by the sponsor, which was a naïve 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 naïve ITC showed 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 low number of patients and wide confidence intervals.
- pERC discussed the importance of therapeutic drug monitoring (TDM) in the management of patients treated with asparaginase as a reliable assessment of asparaginase efficacy. Monitoring asparaginase activity (NSAA levels) is used to initiate and monitor response throughout treatment regimens, as well as distinguishing 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 the routine use of TDM might not always be available or feasible in different settings across Canada, resulting 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 adverse events, since patients above the age of 25 years were not represented in the pivotal trial.

Background

Acute lymphoblastic leukemia and lymphoblastic lymphoma are hematological malignancies characterized by a rapidly progressing transformation and proliferation of lymphoid blasts in the bone marrow, peripheral blood, and other organs. Both conditions are usually described as ALL/LBL because they 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 and close to 75% in adults. ALL/BLL has a bimodal age distribution, with a first peak in childhood (3 out of 4 cases occur in children less than 6 years of age), and a second peak in adults above 60 years of age. In Canada, the incidence of ALL/LBL is 1.3 cases per 100,000 persons of all ages. ALL/LBL has an important impact on the quality of life of patients and caregivers, as well as emotional, financial, and developmental effects. Prognosis is generally poor in adults (5-year survival of 40% to 70%) with older age associated with worse survival, while children and adolescents have better projections (remission in 98% of patients, a 5-year survival above 90%, and long-term event-free survival of 85%).

Asparaginase (L-asparaginase) is an essential part of treatment of ALL/LBL in the induction, consolidation, and intensification phases. It consists of bacterial enzymes derived from either Escherichia coli (E. coli) or Erwinia chrysanthemi (Erwinia). Given the non-human 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 the clinical evolution and outcomes of patients. Also is the potential for silent inactivation – the formation of neutralizing antibodies and reduced asparaginase activity in the absence of clinical hypersensitivity symptoms. Erwinia-derived asparaginase 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 post-market in 2009 only available via an exceptional importation Tier 3 designation.

Crisantaspase recombinant has been approved by Health Canada as a component of a multi-agent 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 Erwinia asparaginase. It is available as a solution for intramuscular (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 six 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 one single arm study in adult and pediatric patients with ALL or LBL
- patients perspectives gathered by one patient group, the Leukemia & Lymphoma Society of Canada (LLSC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with ALL and LBL
- input from two clinician groups, including the Ontario Health-Cancer Care Ontario (OH-CCO), Hematology Cancer Drug Advisory Committee, and the Pediatric Oncology Group of Ontario (POGO)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

One patient group, the Leukemia & Lymphoma Society of Canada (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/weakness (68% of the total respondents) and loss of appetite or weight loss (45% of respondents) as issues to have a significant impact on quality of life. Disease symptoms had a significant impact on respondents' ability to work, exercise, and continue daily activities (64% of respondents). Also, significant impacts on stress/anxiety and problems concentrating due to disease symptoms were reported by 68% and 64% of 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 one respondent who reported experience with crisantaspase recombinant reported manageable side effects and indicated 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/LBL include maximizing cure rates while minimizing short- and long-term side effects, improving HRQoL and reducing caregiver burden. Pegylated E.coli derived asparaginases (pegaspargase) are the mainstay asparaginase treatment option. Clinical evident hypersensitivity reactions to E.coli-derived asparaginase occur in 10% to 15% of patients. 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/LBL, discontinuation of asparaginase therapy would likely lead to inferior survival outcomes and that switching to Erwinia asparaginase would be the next best option. The global supply of Erwinia asparaginase has been limited due to manufacturing difficulties, highlighting the need for a more reliable supply of Erwinia-derived asparaginase.

The clinical experts indicated that the place in therapy of crisantaspase recombinant should be used as a component of a multi-drug regimen for the treatment of ALL/LBL in patients who have developed a documented hypersensitivity reaction or silent inactivation to E. coli-derived asparaginase. The experts also noted that 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 nadir serum asparaginase activity (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/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, therapeutic drug monitoring (TDM) should be performed if available. According to clinical experts, the potential reasons for discontinuing treatment with Crisantaspase include: 1) development of hypersensitivity reaction or silent inactivation to the drug, 2) development of

other types of toxicities (e.g., pancreatitis, thrombosis, and hepatotoxicity), 3) evidence of disease relapse, or 4) 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 these drugs should only be safely given in the inpatient or outpatient hospital setting with immediate availability of suitably trained personnel who can acutely assess the severity of adverse events and provide emergency interventions as required.

Clinician group input

Two clinician groups provided input for this CADTH submission. The Ontario Health-Cancer Care Ontario (OH-CCO), Hematology Cancer Drug Advisory Committee, and the Pediatric Oncology Group of Ontario (POGO). Both groups obtained advice by interviewing clinical experts in the field of cancer, with a focus for this CADTH submission on ALL/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 multi-agent chemotherapy for patients with ALL/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 currently Erwinia is the only available choice for this purpose but there is a short supply and unavailability for Canadian patients and clinicians. The clinician groups agreed that this situation has the risk of creating 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. 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 under Health Canada Exceptional Importation under Tier 3 Drug Shortage designation and is currently being re-evaluated by Health Canada after post-market cancellation in 2021.	*Comment from the drug programs to inform pERC deliberations.*
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. In order 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 three times per week at dosage of 25mg/m^2 IM on Mondays and Wednesdays and 50mg/m^2 IM on Fridays.	*Comment from the drug programs to inform pERC deliberations.*

Drug Program Implementation Questions	Clinical Expert Response
Care Provision Issues	
Erwinase is under Health Canada review. If supply becomes available, under what circumstances would Rylaze® be preferred over Erwinase® (and vice-versa)?	The clinical experts indicated that preference for Rylaze over Erwinase (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 Rylaze over Erwinase if Rylaze is more expensive. They indicated that this may result in off-label use of Rylaze (25 mg/m^2 on Friday rather than 50 mg/m^2). The pERC notes that, since the safety profile seems to be similar, price will play an important role in this decision if there is no evidence of superiority of one over the other.

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/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 endpoint was measured with the asparaginase activity (with NSAA levels ≥ 0.1 international unit [IU]/mL as a meaningful threshold) assessed at 48-h and 72-h. The study was initiated on 27 December 2019 and the data cut-off for the available analysis was 19 July 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, Friday (MWF) 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 receiving a dosing schedule of 25 mg/m^2 on Mondays and Wednesdays and 50 mg/m^2 on Fridays, which is the approved HC indication. The population were of young age (range 3 to 25 years of age), and most (46 of 51, 90%) were diagnosed with ALL. Grade ≥3 allergic reaction to previous E.coli-derived asparaginase occurred in 44 of 51 patients, with 1 silent inactivation, and 6 allergic reaction 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 / minimal residual disease, HRQoL, and serum asparaginase activity (serum NSAA levels). Of these endpoints, only NSAA and harms were available from the pivotal trial. The serum asparaginase activity levels are a surrogate marker for asparagine depletion, and a NSAA level ≥ 0.1 IU/mL 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 dose of cohort 1c (25 [MW], 50[F], mg/m2) reached values above the 0.1 IU/mL threshold for both the last 48 hours (mean 0.65 IU/mL [95% CI 0.53, 0.77]) and the last 72 hours (mean 0.46 IU/mL [95% CI 0.34, 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, 100.0]) at the last 48 hours timepoint (achieving the sponsor's threshold for efficacy of 90%) and 44 of 49 patients (89.8% [95% CI 81.2, 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, SAEs, and WDAEs. 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 19 July 2021, a total of 167 patients (33 in Cohort 1a [IM 25 mg/m2 MWF], 83 in Cohort 1b [IM 37.5 mg/m2 MWF], and 51 in Cohort 1c [25 (MW)/50 (F) mg/m2]) were included in the Safety Analysis Set for Part A (IM) of the study. The focus on this report is the Cohort 1c since this group include the dose approved by Health Canada.

For Cohort 1c, a total of 49 of 51 (96.1%) of 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% of patients [27/51]), platelet count decreased (45.1% [23/51]), neutrophil count decreased (47.1% [24/51]), and vomiting (33.3% [17/51]). In the whole IM cohort, these numbers were similar, with anemia (53.3% of patients [89/167]), platelet count decreased (43.7% [73/167]), neutrophil count decreased (43.1% [72/167]), and vomiting (42.5% [71/167]). These and other AEs, such as pyrexia, fatigue, febrile neutropenia, white blood cell count decreased, stomatitis, increased ALT, were considered by the clinical experts consulted by CADTH of common occurrence in all patients with ALL/LBL treated with asparaginase as part of a multicomponent chemotherapy regimen. The clinical experts indicated that many of the AEs were likely resulting from 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 serious AE at the time of the data cut-off of 19 July 2021. The most common adverse events (in ≥5% of patients) were febrile neutropenia, anemia, gastrointestinal disorders, pyrexia, stomatitis, and sepsis. As with AEs, these were considered by the clinical experts within the expected frequency and part of the ALL/LBL therapy. No deaths occurred in the Cohort 1c, and a total of 3 of 167 patients (1.8%) had a fatal event, 1 happening in Cohort 1a, 2 in Cohort 1b.

Among the notable harms, allergic reactions (hypersensitivity and anaphylaxis) occurred in 18 (35.3%) of patients in Cohort. The most frequently reported events related to allergic reactions in Cohort 1c included rash (7.8% of patients [4/51]); dermatitis (7.8% [4/51]); and allergic transfusion reaction (7.8% [4/51]). As of the data cut-off date (19 July 2021), 6 patients of 51 in the Cohort 1c (11.8%) had suffered from pancreatitis. Thrombosis occurred only in 1 patient of the 51 included in Cohort 1c. Hepatic toxicity was observed in 13 of 51 patients (25.5%) in Cohort 1c group consisting all of elevated measured levels of ALT, AST, and bilirubin. Hypertriglyceridemia occurred in 6 of the 51 patients (11.8%) in the Cohort 1c.

Critical Appraisal

The main limitation of the included study is the single arm (non-comparative) 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 (Erwinia-derived asparaginase) 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 Erwinia-derived asparaginase 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/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- 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 a measurable asparaginase activity with NSAA above a threshold of 0.1 IU/mL, previously set as an important limit of clinical importance. This endpoint, however, is used and should be interpreted as a surrogate for important clinical outcomes.

Indirect Comparisons

Description of studies

One sponsor-submitted indirect treatment comparison (ITC)17 comparing crisantaspase recombinant and EDA was included. The body of evidence in this ITC consisted of two single-arm studies, one of crisantaspase recombinant and the other of EDA. Since an NMA or other population-adjusted ITCs were unfeasible, the analysis was achieved through a naïve comparison of the single treatment arm from each study and calculation of 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 ALL patients, and no patients with LBL patients. The outcomes evaluated are the proportion of patients reaching an NSAA level ≥ 0.1 IU/mL 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 / minimal residual disease, HRQoL) only the NSAA levels, measured as a proportion of patients reaching a 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 a NSAA level ≥ 0.1 IU/mL 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 a NSAA level ≥ 0.1 IU/mL in the last 72-hour assessment time while 38 of 43 (88.4%) of patients in the EDA study reached this level threshold (OR = 1.16; 95% CI: 0.31 to 4.31).

No other efficacy endpoints 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 proportion of patients with increased ALT level (grade 3 or 4) thrombosis, 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 six patients (11.8%) developed pancreatitis in the crisantaspase recombinant trial, in comparison to one patient in the EDA trial (1.8%). [redacted]Of the 8 patients who developed drug hypersensitivity in the EDA trial, it was reported that five of these patients (9% of 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 the 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 eligible courses to date.

Critical Appraisal

The main limitation of the indirect treatment comparison is mostly due to the characteristics of the individual studies conforming the body of evidence. The ITC is achieved through a naïve comparison of each treatment arm from each study, since performing a NMA or a population-adjusted ITC was not feasible due to the small sample size of each single-arm trial. 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 large number of events in a small number of patients. The same limitations apply 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 definitions were used for AEs across the trials, and differences in inclusion criteria may have biased the naïve 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 generalizable to the Canadian population and clinical practice for the specific question and indication assessed in this review. Some differences were noticed such as differences in the condition included (for instance, no LBL patients in the EDA study) and lack of adult patients (≥25 years old) representation in both studies.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: 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) of an E. coli-derived asparaginase. The population was split into two subgroups based on age: children and young adults (up to age 25 years); and, adult patients, aged 25+ years.
Treatment	Crisantaspase recombinant
Dose regimen	25 mg/m^2 of BSA on Monday and Wednesday and 50 mg/m2 on Friday for a total of six 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 four courses) in the pediatric and young adult population (mean BSA: 0.97 m^2) $43,676 per 2-week course ($174,706 for four courses) in adults over 25 years (mean BSA: 1.95 m^2).
Comparators	Base case: *Erwinia* L-asparaginase (Erwinia-derived asparaginase, EDA) Scenario: Best supportive care (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 non-naïve 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 pegasparaginase 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 over 25 years old were thus not assumed to experience remission of ALL/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 a 2nd line asparaginase; the relative efficacy of EDA compared to crisantaspase recombinant; and, the decreased utility values implemented for older adult patients in Years 3+. • 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; ICER = incremental cost-effectiveness ratio; 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 NIHB 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 (Ph) positive ALL, and the future availability of EDA is uncertain.

CADTH corrected the NIHB and provincial populations to avoid double counting. CADTH also conducted a series of scenario analyses exploring the impact of adjusting treatment duration, assuming Ph-positive adults with ALL would not receive asparaginase, assuming the future supply of EDA will only be sufficient for half of Canadian patients 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+ hypersensitivity reaction would be $772,040 in Year 1, $908,555 in Year 2, and $1,048,073 in Year 3, for a three-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+ 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 three-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.

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.

Meeting date: January 11, 2023

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None