DRUG NAME: Crisantaspase recombinant

SYNONYM(S): JZP-458[1], recombinant *Erwinia* asparaginase[1], L-asparaginase (*Erwinia*)[1]

COMMON TRADE NAME(S): RYLAZE®

CLASSIFICATION: antitumour antibiotic

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Crisantaspase is a recombinant form of *Erwinia* asparaginase, an enzyme that catalyzes the conversion of L-asparagine into L-aspartic acid and ammonia. L-asparagine is an amino acid that is essential for the synthesis of protein, RNA, and DNA. Leukemic cells are unable to synthesize adequate amounts of L-asparagine on their own and rely on extracellular sources for DNA synthesis and survival. The sustained depletion of plasma asparagine results in the death of leukemic cells and is thought to be the basis of the pharmacologic effect of asparaginase. L-asparaginase is cell-cycle specific for the G1 phase. Crisantaspase recombinant is an immunosuppressive agent.[2]

Crisantaspase recombinant has an identical amino acid sequence to native *Erwinia* asparaginase. It is derived from a *Pseudomonas fluorescens* expression platform and is expected to have minimal immunologic cross-reactivity to *E. coli* derived asparaginase preparations.[3]

Comparison table of asparaginase products by source and availability

***E. coli*-derived Asparaginase**	
Asparaginase (KIDROLASE)	withdrawn from Canadian market
Pegaspargase (ONCASPAR)	pegylated conjugate of E. coli-derived asparaginase (attached to polyethylene glycol)
Calaspargase pegol (ASPARLAS)	pegylated conjugate of E. coli-derived asparaginase (attached to monomethoxy-polyethylene glycol)
***Erwinia chrysanthemi*-derived Asparaginase**	
Asparaginase-erwinia (ERWINASE)	withdrawn from Canadian market
Crisantaspase recombinant (RYLAZE)	recombinant asparaginase (identical to *Erwinia chrysanthemi*-derived asparaginase)

PHARMACOKINETICS:

Absorption	T_{max} = 13.7 h; absolute availability with IM administration = 37%	
Distribution	low Vd suggests that distribution is limited to the central vascular compartment[4]	
	cross blood brain barrier?	does not appear to cross the blood brain barrier; CSF asparagine depletion has been demonstrated as a result of plasma asparaginase depletion[5]
	volume of distribution	2.16 L
	plasma protein binding	no information found
Metabolism	expected to be metabolized into small peptides by catabolic pathways	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found

Developed: 1 January 2025
Revised:

Excretion	linear elimination expected with one compartment model[3]	
	urine	no information found
	feces	no information found
	terminal half life	19.1 h
	clearance	0.5 L/h
Ethnicity	Black/African American patients had 29% lower clearance which may increase serum asparaginase activity compared to White and Asian patients[6]	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Leukemia, acute lymphoblastic

*Lymphoma, non-Hodgkin

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of anaphylaxis or serious hypersensitivity reaction to *Erwinia* asparaginase therapy[2]
- history of serious pancreatitis, serious hemorrhagic events, or serious thrombosis with previous L-asparaginase therapy[2]

Caution:

- crisantaspase recombinant is ***not interchangeable*** with other asparaginase formulations as they differ in concentration and dosing[2]
- crisantaspase recombinant is associated with increased hepatotoxicity and should be avoided in patients with ***severe hepatic impairment***[6]
- ***sinusoidal obstruction syndrome (SOS)*** *(aka* ***hepatic veno-occlusive disease***) has been reported; use caution in patients with pre-existing liver disease or history of SOS[6]
- ***premedication*** with acetaminophen, H1-blocker, and H2-blocker +/- corticosteroid prior to administration may decrease the risk and severity of infusion and hypersensitivity reactions; if using premedications, consider monitoring asparaginase activity levels[6-9]
- potential for ***immunogenicity*** exists; consider monitoring for asparaginase activity[2]
- ***tumour lysis syndrome*** may result in uric acid nephropathy with asparaginase products; closely monitor uric acid levels, particularly during induction therapy[10,11]
- concurrent administration of ***live vaccines*** may increase the risk of severe infections[10]

Special populations: The risk of certain adverse effects from asparaginase (e.g., hepatotoxicity, thrombosis, and pancreatitis) is increased in patients over 18 years of age.[12]

Carcinogenicity: No studies have been conducted.

Mutagenicity: No studies have been conducted.

Fertility: No studies have been conducted with crisantaspase recombinant. In animal studies with *Erwinia* asparaginase, no impact on male or female fertility were observed. Decreased sperm count was observed in male test subjects.[6]

Pregnancy: No studies have been conducted with crisantaspase recombinant. In animal studies with *Erwinia* asparaginase, intramuscular administration of asparaginase during the period of organogenesis resulted in structural abnormalities and embryo-fetal mortality. Increased post-implantation loss, reduction in the number of live fetuses, and structural abnormalities were observed at exposures less than those seen following human clinical exposure.[6] In

Developed: 1 January 2025
Revised:

females of childbearing potential, pregnancy tests are recommended prior to starting treatment and contraception is recommended during treatment and for 3 months after the last dose. Crisantaspase recombinant may impair the hepatic clearance of oral contraceptives; alternative contraceptive measures are recommended.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 2 weeks after the last dose.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[9] **Incidence data in the Side Effects table is mostly based on data from pediatric clinical trials with crisantaspase recombinant in combination regimens.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	febrile neutropenia (severe 28%)
cardiac	sinus tachycardia (16%, severe 2%)
gastrointestinal	*emetogenic potential:* low[13]; in pediatric patients, minimal (IM route) or high (IV route)[9,14]
	abdominal pain (26%, severe 2%)
	constipation (14%, severe 2%)
	diarrhea (24%, severe 2%)
	gastritis (6%, severe 2%)
	gastroesophageal reflux disease (6%)
	nausea (35%, severe 6%)
	pancreatitis (7-20%, severe 6-8%)[2,6]; see paragraph following **Side Effects** table
	stomatitis (28%, severe 4%)
	vomiting (20-33%, severe 4%)[2,3]
general disorders and administration site conditions	*extravasation hazard:* none[15]
	dehydration (12%, severe 6%)[6]
	fatigue (22%)
	gait disturbance (6%)
	injection site reaction (8%)
	pyrexia (20%)
hepatobiliary	***sinusoidal obstruction syndrome*** (aka veno-occlusive disease); see paragraph following **Side Effects** table
immune system	***antibody development*** (47%)[6]; see paragraph following **Side Effects** table
infections and infestations	infection, including viral, bacterial, and fungal infection[6]
	sepsis (severe 10%)

Developed: 1 January 2025
Revised:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
injury, poisoning, and procedural complications	contusion (14%)
	hypersensitivity, including anaphylaxis (29%, severe 6%); see paragraph following **Side Effects** table
investigations	activated partial thromboplastin time prolonged (severe 6%)
	amylase/lipase increase (20%, severe 8%)[6]
	antithrombin III decrease (6%)
	blood bilirubin increase (8%, severe 4%)
	creatinine increase (6%)
	fibrinogen decrease
	transaminase increase (22%, severe 8%)
	weight loss (14%, severe 4%)
metabolism and nutrition	decreased appetite (28%, severe 6%)
	dehydration (12%, severe 6%)
	hyperammonemia; see paragraph following **Side Effects** table
	hyperglycemia (12%, severe 4%); see paragraph following **Side Effects** table
	hypertriglyceridemia (12%, severe 2%)
	hypoalbuminemia (6%)
	hypocalcemia (8%, severe 2%)
	hypokalemia (22%, severe 8%)
	hyponatremia (6%)
musculoskeletal and connective tissue	arthralgia (6%)
	back pain (12%, severe 2%)
	muscular weakness (6%, severe 2%)
	pain in extremity (16%, severe 2%)
nervous system	dizziness (8%)
	headache (22%)
	hyperammonemic encephalopathy[6]
	neurotoxicity **(**posterior reversible encephalopathy syndrome, CNS depression, and seizure are reported with asparaginase)[12]
	paresthesia (8%)
	peripheral neuropathy (6-15%)[6]
psychiatric	agitation/irritability
	anxiety (10%, severe 2%)
renal	acute kidney injury[6]
	cough (14%)

Developed: 1 January 2025
Revised:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
respiratory, thoracic, and mediastinal	epistaxis (10%, severe 4%)
	nasal congestion (8%)
	oropharyngeal pain (10%)
	rhinorrhea (8%)
skin and subcutaneous tissue	drug eruption (6%)
	dry skin (10%)
	pruritus (6%)
	rash (8%)
	skin hyperpigmentation (6%)
vascular (see paragraph following **Side Effects** table)	***hemorrhage*** (26%, severe 2%)
	hypertension (14%)
	hypotension (8%, severe 4%)
	thrombotic events (4%, severe 2%)[2,6]; includes sagittal sinus thrombosis, pulmonary embolism, and deep vein thrombosis[12]

Adapted from standard reference[2] unless specified otherwise.

Elevated ***ammonia*** levels are an expected side effect of asparaginase treatment based on the mechanism of action of the enzyme. Asparaginase catabolizes asparagine to aspartic acid and ammonia, and secondarily converts glutamine to glutamate and ammonia. Many patients with reported asparaginase-induced hyperammonemia are asymptomatic. Severe complications and fatal outcomes have occurred.[6] Consider monitoring ammonia levels in the presence of symptoms such as nausea, vomiting, lethargy, and irritation.[7,16]

As with all therapeutic proteins, there is the potential for immunogenicity.[2] Exposure to asparaginase can trigger the development of ***anti-asparaginase antibodies***, which have been *a*ssociated with ***reduced asparaginase activity.*** Overt clinical hypersensitivity is considered a strong indicator that a patient has developed anti-asparaginase antibodies. However, the formation of these neutralizing antibodies has also been demonstrated in the absence of overt hypersensitivity and this phenomenon is known as silent inactivation. Continuing treatment with the same asparaginase formulation in the setting of either overt allergy or silent inactivation may be therapeutically ineffective. Consider monitoring asparaginase activity levels for the detection of silent inactivation and also in the setting of hypersensitivity to confirm continued activity of the treatment.[8,17]

Glucose intolerance can occur in patients receiving asparaginase products when alterations in endocrine pancreatic function become expressed as abnormal glucose metabolism. Glucose intolerance may be irreversible. Diabetic ketoacidosis, hyperosmolar hyperglycemia, and clinical hyperglycemia have been reported with other asparaginase products. Treatment with insulin may be required. Monitor patients for signs and symptoms of hyperglycemia regularly throughout treatment.[2,17]

Hemorrhage and serious ***thrombotic events*** have been reported in patients treated with asparaginase products. Hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Evaluate coagulation parameters in patients with signs and symptoms of hemorrhage. Replacement therapy with clotting factor may be required. Permanently discontinue crisantaspase recombinant if uncontrolled bleeding or a life-threatening thrombotic event occur.[2,6]

Hepatotoxicity, including ***sinusoidal obstruction syndrome (SOS)*** (aka veno-occlusive disease) has been reported in patients treated with crisantaspase recombinant in combination with standard chemotherapy.[6] Crisantaspase recombinant is not recommended in patients with severe hepatic impairment. Signs and symptoms of

Developed: 1 January 2025
Revised:

SOS may include rapid weight gain, fluid retention with ascites, hepatomegaly, and rapid increase of bilirubin. Monitor bilirubin and transaminases throughout treatment. Discontinue treatment if total bilirubin >10 x ULN or other signs of serious liver toxicity, including SOS, are present.[2,6]

With asparaginase class products, a range of ***hypersensitivity reactions*** have been reported such as angioedema, lip swelling, eye swelling, erythema, decreased blood pressure, bronchospasm, dyspnea, pruritus, and rash. Hypersensitivity reactions are reported in 29% of patients receiving crisantaspase recombinant, including life-threatening anaphylaxis.[2] The median number of doses received before the onset of hypersensitivity is 12 doses (range 1-64 doses) and the most observed reaction is maculopapular rash.[6] ***Premedication*** with acetaminophen, H1-blocker, and H2-blocker +/- corticosteroids may decrease the risk and severity of infusion and hypersensitivity reactions. If using premedications, consider monitoring asparaginase activity levels.[6-8] Be prepared to treat anaphylaxis with each administration and manage reactions according to the severity of the symptoms. Permanently discontinue crisantaspase recombinant for grade 3 or 4 hypersensitivity reactions.[2]

Pancreatitis has been reported in up to 20% of patients receiving crisantaspase recombinant, with 6-8% reported as grade 3 or 4 in severity.[2,6] Hemorrhagic or necrotizing pancreatitis can occur and can be life-threatening.[12] Serum amylase and/or lipase can identify early signs of pancreatic inflammation and glucose and triglyceride levels should be monitored regularly during treatment. Persistent and/or severe abdominal pain that may radiate to the back is the characteristic symptom of pancreatitis and may be fatal if left untreated. Elevated amylase or lipase without symptomatic pancreatitis has been reported in 13% of patients treated with crisantaspase recombinant.[6] Hold crisantaspase recombinant for mild pancreatitis until the signs and symptoms subside and amylase and/or lipase levels return to normal. After resolution of mild pancreatitis, crisantaspase recombinant may be resumed. Permanently discontinue treatment if necrotizing or hemorrhagic pancreatitis occurs.[2,6]

INTERACTIONS:

No formal pharmacokinetic drug interaction studies have been conducted. However, crisantaspase recombinant may[10,12]:

- reduce the metabolism/clearance of protein-bound drugs and/or increase their toxicity by decreasing serum proteins,
- reduce the metabolism/clearance of other drugs due to its hepatotoxicity,
- negate the action of drugs requiring cell division for their effect by inhibiting protein synthesis and cell division,
- lead to fluctuating coagulation factors and should be used cautiously with drugs having either procoagulant or anticoagulant effects,
- increase the CNS toxicity of other neurotoxic drugs,
- work synergistically with methotrexate and cytarabine if administered subsequent to them,
- be less effective if administered prior to methotrexate or cytarabine due to a weak antagonistic effect,
- increase exposure to glucocorticoids by decreasing glucocorticoid elimination,
- increase the risk of glucocorticoid-induced osteonecrosis in children >10 years of age, with a higher incidence seen in girls.

SUPPLY AND STORAGE:

Injection**:** Jazz Pharmaceuticals Canada Inc. supplies crisantaspase recombinant as 10 mg single-use (preservative free) vials in a concentration of 20 mg/mL. Refrigerate. Store in original packaging to protect from light. Do not shake.[2]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Developed: 1 January 2025
Revised:

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular[2]	maximum volume of 2 mL to be injected at a single site; use multiple injection sites for volumes greater than 2 mL
Direct intravenous	no information found
Intermittent infusion	has been used[12] (increased risk of hypersensitivity[6])
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intramuscular:	2 weeks[2,3]	25 mg/m^2 IM for one dose on Monday and Wednesday, and 50 mg/m^2 on Friday of each week (total 6 doses) (total dose per cycle: 200 mg/m^2)
	2 weeks[6]	25 mg/m^2 IM for one dose every 48 hours (total 7 doses) (total dose per cycle: 175 mg/m^2)

Developed: 1 January 2025
Revised:

BC Cancer usual dose noted in ***bold, italics***

Cycle Length:

Due to differing pharmacokinetic profiles, the dose of crisantaspase recombinant cannot be substituted 1:1 with pegylated asparaginase products. See table below for the recommended dose replacement[2,6] and/or modify according to protocol by which patient is being treated.

To replace a planned dose of a pegylated asparaginase with crisantaspase recombinant[6]:

Crisantaspase recombinant dosing regimen	To replace one dose of ***calaspargase pegol*** (3 weeks of asparaginase coverage)	To replace one dose of ***pegaspargase*** (2 weeks of asparaginase coverage)
25 mg/m^2 on Mon/Wed and 50 mg/m^2 on Fri	requires 9 doses of crisantaspase recombinant	requires 6 doses of crisantaspase recombinant
25 mg/m^2 every 48 hrs	requires 11 doses of crisantaspase recombinant	requires 7 doses of crisantaspase recombinant

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure: no information found

Dosage in hepatic failure: mild/moderate impairment: no information found
severe impairment: avoid[2]

Dosage in dialysis: no information found

Children:

	Cycle Length:	
Intramuscular:	2 weeks[2,3,9]	≥1 month of age: 25 mg/m^2 IM for one dose on Monday and Wednesday, and 50 mg/m^2 on Friday of each week (total 6 doses) (total dose per cycle: 200 mg/m^2)
	2 weeks[6,9]	≥1 month of age: 25 mg/m^2 IM for one dose every 48 hours (total 7 doses) (total dose per cycle: 175 mg/m^2)

Developed: 1 January 2025
Revised:

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Asparaginase (Erwina [Recombinant]). Lexi-Comp Inc., Available at: http://online.lexi.com. Accessed July 2, 2024
2. Jazz Pharmaceuticals Canada Inc. RYLAZE® product monograph. Mississauga, Ontario; September 2 2022
3. Maese L, Loh ML, Choi MR, et al. Recombinant Erwinia Asparaginase (JZP458) in Acute Lymphoblastic Leukemia: Results from the Phase 2/3 AALL1931 study. Blood 2023;141(7):704-712
4. European Medicines Agency. Assessment Report - ENRYLAZE (crisantaspase). Amsterdam, The Netherlands; July 20 2023
5. Gentili D, Conter V, Rizzari C, et al. L-Asparagine Depletion in Plasma and Cerebro-Spinal Fluid of Children with Acute Lymphoblastic Leukemia During Subsequent Exposures to Erwinia L-asparaginase. Annals of Oncology 1996;7(7):725-730
6. Jazz Pharmaceuticals Inc. RYLAZE® full prescribing information. Palo Alto, CA, USA; April 15 2024
7. COG Pharmacy Steering Committee and COG Pharmacist. Parenteral and Oral Chemotherapy Administration Guidelines Used by the Children's Oncology Group. Version 12. June 11 2024
8. van der Sluis, I. M., Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. Haematologica 2016;101(3):279-285
9. Kendrick, Jennifer. Clinical Pharmacy Specialist, Children's and Women's Health Centre of British Columbia. Personal Communication - crisantaspase recombinant. December 3 2024
10. Servier Canada Inc. ASPARLAS® product monograph. Laval, Quebec; March 8 2024
11. CGF Pharmatec for Jazz Pharmaceuticals France SAS. ERWINASE® product monograph. Montreal, Quebec; August 30 2016
12. Jazz Pharmaceuticals Ireland Ltd. ENRYLAZE® Summary of Product Characteristics. Dublin, Ireland; Oct 5 2023
13. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 2022
14. Sing EPC, Robinson PD, Flank J, et al. Classification of the Acute Emetogenicity of Chemotherapy in Pediatric Patients: A Clinical Practice Guideline. Pediatric Blood & Cancer 2011;57(2):191-198
15. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; March 1 2021
16. Lee A, Eldem I, Altintas B, et al. Treatment and outcomes of symptomatic hyperammonemia following asparaginase therapy in children with acute lymphoblastic leukemia. Molecular Genetics and Metabolism 2023;139(3)
17. Stock W, Douer D, DeAngelo DJ, et al. Prevention and Management of Asparaginase/pegasparaginase-Associated Toxicities in Adults and Older Adolescents: Recommendations of an Expert Panel. Leuk.Lymphoma 2011;52(12):2237-2253

Developed: 1 January 2025
Revised: