Drug Monograph

A - Drug Name

crisantaspase recombinant

COMMON TRADE NAME(S): Rylaze™

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B - Mechanism of Action and Pharmacokinetics

Crisantaspase recombinant hydrolyzes extracellular L-asparagine, an amino acid that is essential for protein synthesis by leukemic cells, which are unable to synthesize asparagine and depend on an exogenous source, and results in cytotoxicity.

Crisantaspase recombinant is a recombinant form of Erwinia asparaginase. It is expressed in *Pseudomonas fluorescens* with an identical amino acid sequence to native Erwinia asparaginase. This is antigenically distinct from *E. coli*-derived asparaginase and therefore can be used as an alternative in patients who have a documented hypersensitivity (reaction and/or silent inactivation) to *E. coli*-derived asparaginase products.

Absorption	Exposure increases proportionally over a dosing range from 12.5 to 50 mg/m^2.	
	Bioavailability	37% (IM)
	T max	13.7 hours
Metabolism	Crisantaspase recombinant is expected to be metabolized by catabolic pathways into small peptides.	
Elimination	Half-life	19.1 hours (IM)

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C - Indications and Status

Health Canada Approvals:

- Acute lymphoblastic leukemia (ALL)*
- Lymphoblastic lymphoma (LBL)*

Refer to the product monograph for a full list of approved indications.

Other Uses:

- Mixed/biphenotypic leukemia*

*For use in patients who have a documented hypersensitivity (reaction and/or silent inactivation) to *E. coli*-derived asparaginase products

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D - Adverse Effects

Emetogenic Potential: Minimal

The following adverse effects were reported (≥5% incidence) in a small Phase II/III open-label trial of pediatric and adult patients with ALL or LBL, who had developed hypersensitivity to *E. coli*-derived asparaginase (pegaspargase), in combination with other chemotherapy. Severe and life-threatening adverse effects from post-marketing or other sources may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial/venous thromboembolism (4%) (2% severe)	E
	Hypertension (14%)	E
	Hypotension (8%)	E
	Tachycardia (16%)	E
Dermatological	Rash, pruritus (8%)	E
Gastrointestinal	Abdominal pain (26%)	E
	Anorexia, weight loss (28%)	E
	Constipation (14%)	E

	Dehydration (12%)	E
	Diarrhea (24%)	E
	Gastroesophageal reflux disease (6%)	E
	Mucositis (28%)	E
	Nausea, vomiting (35%) (6% severe)	I E
General	Fatigue (22%)	E
Hematological	Hemorrhage (2%) (severe)	E
	Other - Prolonged PT/aPTT, ↓ antithrombin III, hypofibrinogenemia (6%)	E
Hepatobiliary	↑ Bilirubin (8%)	E
	↑ LFTs (22%) (8% severe)	E
	Pancreatitis (12%) (8% severe)	E
Hypersensitivity	Hypersensitivity (29%) (2% anaphylaxis)	I E D
Injection site	Injection site reaction (8%)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (22%) (↓ K, Ca, Na)	E
	Hyperglycemia (12%)	E
	↑ Triglycerides (12%)	E
Musculoskeletal	Musculoskeletal pain (16%)	E
Nervous System	Dizziness (8%)	E
	Headache (22%)	E
	Paresthesia (8%)	E
Renal	Creatinine increased (6%)	E
Respiratory	Cough (14%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

When given in combination with chemotherapy, the most common side effects for crisantaspase recombinant include nausea, vomiting, hypersensitivity, anorexia, weight loss, mucositis, abdominal pain, diarrhea, fatigue, headache, ↑ LFTs and abnormal electrolyte(s).

In clinical trials, the onset of **hypersensitivity** occurred after a median of 12 crisantaspase recombinant IM doses (range 1-64 doses). The most common reaction was rash (including maculopapular rash). Severe reactions were reported in 6% of patients, including anaphylaxis (2%).

Hypersensitivity reactions were higher in patients who received IV crisantaspase recombinant than IM; thus, the IV route of administration is not recommended.

Bleeding was reported in trials (26%) but the most commonly observed reactions were bruising and nose bleeds. **Hemorrhage,** in patients treated with L-asparaginase-class of products, may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT) and hypofibrinogenemia. Patients should be evaluated for coagulopathy and receive appropriate treatment as needed.

Pancreatitis, including acute pancreatitis, was observed in clinical trials and may be severe. Hemorrhagic or necrotizing pancreatitis has been reported with asparaginase class products.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Premedications (prophylaxis for administration-related reactions)

To be given 30-60 minutes prior to crisantaspase recombinant administration:

- acetaminophen
- H1 receptor blocker (e.g. diphenhydramine)
- H2 receptor blocker (e.g. famotidine)

Adults:

Risk of medication error: Different asparaginase formulations are **not interchangeable** and dosing schedules are different. Confirm the formulation carefully against the regimen used before prescribing, dispensing and administration.

Intramuscular: 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

Refer to protocol by which patient is being treated for cycle frequency. Usually used in combination with other cytotoxic drugs.

Dosage with Toxicity:

Discontinue in patients who experience silent inactivation, high grade toxicities, or evidence of disease progression.

Toxicity	Severity	Action
Hypersensitivity	Grade 3 to 4	Discontinue.
Amylase or lipase	> 2 x ULN or Symptomatic pancreatitis	Hold. Restart when amylase and lipase < 1.5 x ULN and symptoms resolve. Discontinue if clinical necrotizing or hemorrhagic pancreatitis is confirmed.
Thrombosis	Uncomplicated	Hold. Treat with appropriate antithrombotic therapy. Consider restart if symptoms resolve, while continuing antithrombotic therapy.
	Severe or life-threatening	Discontinue. Treat with appropriate antithrombotic therapy.
Hemorrhage	Grade 3 to 4	Hold. Evaluate for coagulopathy and consider clotting factor replacement as needed. If clinically appropriate, resume with the next scheduled dose.
Hepatotoxicity	Total bilirubin > 3 to ≤10 x ULN	Hold. Restart when total bilirubin ≤1.5 x ULN.
	Total bilirubin > 10 x ULN	Discontinue.

Dosage with Hepatic Impairment:

Crisantaspase recombinant has not been studied in patients with hepatic impairment.

Dosage with Renal Impairment:

Crisantaspase recombinant has not been studied in patients with renal impairment.

Dosage in the elderly:

There was insufficient data in patients ≥ 65 years of age to determine if there are differences in response compared to younger patients.

Dosage based on gender:

There were no clinically significant differences in the pharmacokinetics of crisantaspase recombinant based on gender.

Dosage based on ethnicity:

Black patients had 29% lower clearance which may increase exposure compared to White and Asian patients.

Children:

Safety and efficacy of crisantaspase recombinant has been established in patients ≥ 1 year of age. There were no clinically significant differences in safety or asparaginase activity based on age (1.4 to 25 years).

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F - Administration Guidelines

Risk of medication error: Different asparaginase formulations **are not Interchangeable** and dosing schedules are different. Confirm the formulation carefully against the regimen used before prescribing, dispensing and administration.

- Crisantaspase recombinant should be is administered by **intramuscular injection only**.
- Do not shake the vial.
- No reconstitution or dilution is required. Withdraw the indicated injection volume into the syringe(s) for injection.
- The maximum volume for injection at a single injection site is 2 mL. Use multiple injection sites if the volume to be administered is > 2 mL.
- Do not inject crisantaspase recombinant into scar tissue or areas that are reddened, inflamed, or swollen.
- Store unopened vials at 2°C to 8°C in the original carton, protected from light.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components, or have had serious hypersensitivity reactions to Erwinia asparaginase, including anaphylaxis
- Patients who have a history of serious pancreatitis, thrombosis or hemorrhagic events during previous asparaginase therapy

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Crisantaspase recombinant is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for **3 months** after the last dose.
  A method of contraception other than oral contraceptives should be used in people who can become pregnant, since an indirect interaction between oral contraception and crisantaspase recombinant cannot be excluded.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects: Unknown

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H - Interactions

No formal drug interaction studies have been conducted with crisantaspase recombinant.

The following interactions were reported with *other formulations of asparaginase*:

AGENT	EFFECT	MECHANISM	MANAGEMENT
Hepatotoxic drugs	↑ hepatotoxicity	Additive	Monitor liver function; use with caution
Drugs requiring hepatic enzyme metabolism	May ↑ toxicity of these agents	Asparaginase may interfere with enzymatic detoxification	Caution
Methotrexate	↓ effect of both drugs when asparaginase given immediately before or concurrently with methotrexate; Enhanced effect of both drugs when asparaginase given after methotrexate	Suppression of asparagine concentrations or cell replication	Refer to protocol by which patient is treated
Cytarabine	↓ effect of asparaginase when asparaginase given immediately before or concurrently with cytarabine; Enhanced effect of asparaginase when asparaginase given after cytarabine	Suppression of asparagine concentrations or cell replication	Refer to protocol by which patient is treated
Immunosuppressants (i.e., cyclosporine, tacrolimus, sirolimus)	↑immunosuppression, risk of lymphoproliferation	Additive	Caution
Phenytoin	↑ risk of seizures	↓ phenytoin uptake; risk of ↑ toxicity or ↓ efficacy of cytotoxics due to metabolism induction	Use other anticonvulsant alternatives
Prednisone	↑hyperglycemia	Additive	Monitor
Vincristine and/or prednisone	↑ vincristine toxicity when vincristine given concurrently or immediately after asparaginase	Unknown	Refer to protocol by which patient is treated

Anticoagulants, including NSAIDs, ASA	↑ risk of bleeding	Changes in coagulation by asparaginase	Use with caution
Serum thyroxine-binding globulin	↓ total serum thyroxine-binding globulin concentration	↓ synthesis of thyroxine-binding globulin in liver	Delay measurement until 4 weeks after end of asparaginase therapy
Live and attenuated live vaccines	↑ risk of severe infections	Immunosuppressive activity of asparaginase	Avoid. Vaccinations with live vaccines should be given at least 3 months after the end of the entire treatment protocol
Oral contraceptives	May ↓ efficacy of oral contraceptives (reported with pegaspargase)	May impair hepatic clearance of oral contraceptives due to asparaginase's hepatotoxic effects	Use alternative contraception method
Glucocorticoids	↑ effects on fibrinogen and ATIII decreases (reported with pegaspargase)	Unknown	Refer to protocol by which patient is treated
Highly protein-bound drugs	↑ toxicity of these drugs (reported with pegaspargase)	Decreased serum proteins	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
LFTs, bilirubin	Baseline, before each cycle, and as clinically indicated
Amylase and lipase	Baseline, before each cycle, and as clinically indicated
Clotting profile (PT, aPTT, fibrinogen, AT III)	Baseline, and as clinically indicated; more frequent in patients at risk of coagulopathies
Blood glucose	Baseline, as clinically indicated and more frequently if patients have diabetes
Trough serum asparaginase level	Refer to local protocol
Clinical toxicity assessment for tumour lysis syndrome, pancreatitis, GI effects, infection, hypersensitivity reactions, thromboembolism/bleeding	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and as clinically indicated
Cholesterol and triglycerides	As clinically indicated
Urinary glucose	As clinically indicated
Albumin levels	As clinically indicated

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Crisantaspase Recombinant - Acute Lymphoblastic Leukemia Lymphoblastic Lymphoma Mixed or Biphenotypic Leukemia

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K - References

CADTH reimbursement review: Crisantaspase recombinant (Rylaze). Canadian Journal of Health Technologies, July 2023 (published online).

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NCI Drug Dictionary: Asparaginase Erwinia chrysanthemi (recombinant)-rywn. Accessed July 17, 2023.

Prescribing information: asparaginase Erwinia chrysanthemi (recombinant)-rywn. Jazz Pharmaceuticals Inc. (USA), November 2022.

Product monograph: crisantaspase recombinant (Rylaze™). Jazz Pharmaceuticals Canada Inc., September 2, 2022.

Recombinant Erwinia asparaginase: Lexicomp drug information. Accessed August 29, 2023.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management

information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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