PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr RYLAZE™

crisantaspase recombinant

Solution for Intramuscular Injection, 10 mg/0.5 mL (20 mg/mL)

Antineoplastic Agent

Jazz Pharmaceuticals Ireland Limited.
5th Floor Waterloo Exchange,
Waterloo Road, Dublin D04 EW57

Imported by:
Jazz Pharmaceuticals Canada Inc.,
4080 Confederation Parkway, Suite 602,
Mississauga, ON L5B 0G1

Date of Initial Authorization:
SEP 02, 2022

Submission Control Number: 257092

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RYLAZE (crisantaspase recombinant) is indicated 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.

1.1 Pediatrics (1 to < 17 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of RYLAZE in pediatric patients 1 year of age or older has been established. Therefore, Health Canada has authorized an indication for pediatric use [see 14 CLINICAL TRIALS].

1.2 Geriatrics (> 65 years of age)

Clinical studies of RYLAZE did not include sufficient number of patients 65 years of age and older to determine whether they respond differently from younger patients.

2 CONTRAINDICATIONS

RYLAZE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis [see 7 WARNINGS AND PRECAUTIONS, Immune].
- Serious pancreatitis during previous asparaginase therapy [see 7 WARNINGS AND PRECAUTIONS, Pancreatic].
- Serious thrombosis during previous asparaginase therapy [see 7 WARNINGS AND PRECAUTIONS, Hematologic].
- Serious hemorrhagic events during previous asparaginase therapy [see 7 WARNINGS AND PRECAUTIONS, Hematologic].
- RYLAZE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Recommended Dosage

The recommended dosage of RYLAZE is 25 mg/m^2 on Monday and Wednesday and 50 mg/m^2 on Friday, administered intramuscularly, for a total of six doses to replace each planned dose of pegaspargase.

Recommended Monitoring and Dosage Adjustment for Adverse Reactions

Monitor patient's bilirubin, transaminases, glucose, and clinical examinations prior to treatment every 2-3 weeks and as indicated clinically during treatment with RYLAZE. If results are abnormal, monitor patients until recovery from the cycle of therapy. If an adverse reaction occurs, modify treatment according to Table 1.

Table 1: Dosage Adjustments

Adverse Reaction	Severity*	Action
Hypersensitivity Reaction [see 7 WARNINGS AND PRECAUTIONS]	Grade 2	• Treat the symptoms.
	Grade 3 to 4	• Discontinue RYLAZE permanently.
Pancreatitis [see 7 WARNINGS AND PRECAUTIONS]	Grade 2 to 4	• Hold RYLAZE for elevations in lipase or amylase > 2 times the ULN, or for symptomatic pancreatitis. • Resume treatment when lipase and amylase are < 1.5 times the ULN and symptoms are resolved. • Discontinue RYLAZE permanently if clinical necrotizing or hemorrhagic pancreatitis is confirmed.
Thrombosis [see 7 WARNINGS AND PRECAUTIONS]	Uncomplicated thrombosis	• Hold RYLAZE. • Treat with appropriate antithrombotic therapy. • Upon resolution of symptoms, consider resuming RYLAZE, while continuing antithrombotic therapy.
	Severe or life-threatening thrombosis	• Discontinue RYLAZE permanently. • Treat with appropriate antithrombotic therapy.
Hemorrhage [see 7 WARNINGS AND PRECAUTIONS]	Grade 3 to 4	• Hold RYLAZE. • Evaluate for coagulopathy and consider clotting factor replacement as needed.

Adverse Reaction	Severity*	Action
		• Resume RYLAZE with the next scheduled dose if bleeding is controlled.
Hepatotoxicity [see 7 WARNINGS AND PRECAUTIONS]	Total bilirubin > 3 times to ≤ 10 times the ULN	• Hold RYLAZE until total bilirubin levels decrease to ≤ 1.5 times the ULN.
	Total bilirubin > 10 times the ULN	• Discontinue RYLAZE and do not make up missed doses.

*Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

4.4 Administration

RYLAZE solution should only be administered by intramuscular injection.

Administer RYLAZE in a clinical setting with resuscitation equipment and other medical support available to appropriately manage anaphylactic reactions.

Visually inspect parenteral drug products for particulate matter, cloudiness, or discoloration prior to administration. If any of these are present, discard the vial. RYLAZE does not contain a preservative.

Use aseptic technique when administering RYLAZE.

- Do not shake the vial.
- Determine the dose, total volume of RYLAZE solution required, and the number of RYLAZE vials needed.
- Withdraw the indicated injection volume of RYLAZE into the syringe(s) for injection.
- Limit the volume of RYLAZE at a single injection site to 2 mL. If the volume to be administered is greater than 2 mL, use multiple injection sites.
- Discard any remaining unused RYLAZE in the single-dose vial.
- Administer RYLAZE within 4 hours of syringe preparation.
  - Rotate injection sites.
  - Do not inject RYLAZE into scar tissue or areas that are reddened, inflamed, or swollen.
- If needed, store the syringe(s) at room temperature for up to 4 hours. The syringe does not need to be protected from light during storage.

5 OVERDOSAGE

There is no specific antidote for an overdose with RYLAZE. If overdose occurs, patients should be treated supportively with appropriate monitoring as necessary.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Intramuscular Injection	Solution for injection / 10 mg crisantaspase recombinant in 0.5 mL (20 mg/mL)	Polysorbate 80, sodium chloride, sodium hydroxide, sodium phosphate dibasic anhydrous, sodium phosphate monobasic monohydrate and trehalose dihydrate.

RYLAZE is a clear to opalescent, colourless to slightly yellow, preservative-free sterile solution supplied in single-dose vials.

Each carton of RYLAZE contains 3 single-dose vials.

7 WARNINGS AND PRECAUTIONS

The safety of RYLAZE described in the WARNINGS AND PRECAUTIONS reflect exposure to RYLAZE at various dosages, including cumulative dosages higher than the recommended and used in combination with chemotherapy in 167 patients in study JZP458-201 (Study data cut-off date was 19th July 2021). These patients received a median of 4 courses of RYLAZE (range: 1-15 courses); 65% of patients received at least four courses.

Endocrine and Metabolism

Hyperglycemia was reported in 16% of patients receiving RYLAZE in clinical trials, and it was severe in 4% of patients [see 8 ADVERSE REACTIONS]. Monitor glucose levels in patients at baseline and periodically during treatment. Treat hyperglycemia as medically indicated.

Hematologic

Thrombosis

Thrombotic events, including sagittal sinus thrombosis and pulmonary embolism, have been reported in 4% of patients following treatment with RYLAZE, and it was severe in 2% of patients.

Discontinue RYLAZE for a thrombotic event and administer appropriate antithrombotic therapy. Consider resumption of treatment with RYLAZE only if the patient had an uncomplicated thrombosis [see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment].

Hemorrhage

Bleeding was reported in 26% of patients treated with RYLAZE, and it was severe in 2% of patients. Most commonly observed reactions were contusion (11%) and nose bleeding (9%).

In patients treated with L-asparaginase class products, hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Consider appropriate replacement therapy in patients with severe or

symptomatic coagulopathy [see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment].

Hepatic

Liver function abnormality occurred in 32% of patients in clinical trials of RYLAZE and it was severe in 17% of patients. The most commonly observed reactions were elevated transaminases (28%), which was severe in 15% of patients, and elevated bilirubin (11%), which was severe in 2% of patients [see 8 ADVERSE REACTIONS].

Evaluate bilirubin and transaminases prior to treatment every 2-3 weeks and as indicated clinically during treatment with RYLAZE. In the event of serious liver toxicity, discontinue treatment with RYLAZE and provide supportive care [see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment].

Pancreatic

Pancreatitis was reported in 7% of patients treated in clinical trials of RYLAZE and was severe in 6% of patients [see 8 ADVERSE REACTIONS]. Hemorrhagic or necrotizing pancreatitis have been reported with asparaginase class products.

Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Discontinue RYLAZE in patients with severe or hemorrhagic pancreatitis. In the case of mild pancreatitis, withhold RYLAZE until the signs and symptoms subside and amylase and/or lipase levels return to normal. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed [see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment].

Immune

Hypersensitivity reactions after the use of RYLAZE occurred in 29% of patients in clinical trials, and it was severe in 6% of patients [see 8 ADVERSE REACTIONS]. The most commonly observed reaction was maculopapular rash (8%) and rash (7%), and no patients experienced severe maculopapular rash or rash. Anaphylactic reaction was observed in 2% of patients.

Hypersensitivity reactions observed with L-asparaginase class products include angioedema, urticaria, lip swelling, eye swelling, rash or erythema, blood pressure decreased, bronchospasm, dyspnea, and pruritus.

Because of the risk of serious allergic reactions, administer RYLAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis [see 4.4 DOSAGE AND ADMINISTRATION, Administration]. Discontinue RYLAZE in patients with serious hypersensitivity reactions [see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment].

Reproductive Health: Female and Male Potential

Nonclinical studies were not conducted to evaluate the potential effects of RYLAZE on reproductive health. However, published data with other asparaginases indicate that RYLAZE can cause embryonic and fetal harm when administered to a pregnant woman [see 7.1.1 WARNINGS AND PRECAUTIONS, Pregnant Women and 16 NON-CLINICAL TOXICOLOGY].

Pregnancy Testing

Pregnancy testing in females of reproductive potential is recommended prior to starting treatment with RYLAZE.

Contraception

Advise females of reproductive potential to avoid becoming pregnant while receiving RYLAZE due to the risks to the fetus. Females should use effective contraceptive methods during treatment and for 3 months after the last dose. Since an indirect interaction between oral contraception and RYLAZE cannot be ruled out, a method of contraception other than oral contraceptives should be used in women of childbearing potential.

- **Fertility**

Nonclinical studies were not conducted to evaluate the potential effects of RYLAZE on fertility. Nonclinical reports of impaired fertility following asparaginase treatment were not identified in the literature. [see 16 NON-CLINICAL TOXICOLOGY].

- **Teratogenic risk**

Nonclinical studies were not conducted to evaluate the potential teratogenicity of RYLAZE. However, published data with other asparaginases indicate that RYLAZE can cause embryonic and fetal harm when administered to a pregnant woman [see 16 NON-CLINICAL TOXICOLOGY].

Driving and Operating Machinery

Based on the adverse reactions of RYLAZE there may be a minor influence on the ability to drive and use machines [see 8.1 ADVERSE REACTIONS, Adverse Reaction Overview].

7.1 Special Populations

7.1.1 Pregnant Women

There are no data on the use of RYLAZE in pregnant women. However, published data with other asparaginases indicates that RYLAZE can cause embryonic and fetal harm when administered to a pregnant woman. RYLAZE should not be used during pregnancy, unless the clinical condition of the woman requires treatment and justifies the potential risk to the fetus.

If the medicinal product is used during pregnancy, or if the patient becomes pregnant while receiving RYLAZE, the woman should be informed of the potential risk to the fetus.

7.1.2 Breast-feeding

It is not known whether RYLAZE is excreted in human milk. Because of the potential for serious adverse reactions in breast-feeding children, advise women not to breast-feed during treatment with RYLAZE and for 2 weeks after the last dose.

7.1.3 Pediatrics (1 to < 17 years of age)

The safety and effectiveness of RYLAZE in the treatment of ALL and LBL have been established in pediatric patients 1 year to < 17 years of age who have developed hypersensitivity to pegaspargase. Use of RYLAZE in these age groups is supported by evidence from a single arm open label study in adults and pediatric patients. The trial included 112 pediatric patients, including 2 infants (1 year to < 2 years old), 79 children (2 years to < 12 years old), and 31 adolescents (12 years to < 17 years old). There were no clinically meaningful differences in safety or nadir serum asparaginase activity across age groups. The safety and effectiveness of RYLAZE have not been established in pediatric patients younger than 1 year of age.

7.1.4 Geriatrics (> 65 years of age)

Clinical studies of RYLAZE did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of RYLAZE was evaluated in a cohort of 51 patients from study JZP458-201 who received RYLAZE intramuscularly at a dosage of 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 [see 14 CLINICAL TRIALS]. RYLAZE was administered as a component of multi-agent chemotherapy.

The study population included patients with a median age of 10 years (range, 1 to 25 years); the majority of patients were male (61%) and white (65%). The patients received a median of 4 courses of RYLAZE (range: 1-11 courses).

The most common adverse reactions (in ≥ 20% of patients) were anemia, thrombocytopenia, neutropenia, nausea, vomiting, decreased appetite, febrile neutropenia, stomatitis, abdominal pain, diarrhea, fatigue, headache, hypokalemia, transaminase increased, white blood cell count decreased and pyrexia. The most common Grade 3 or higher adverse reactions (in ≥ 5% of patients) were neutropenia, thrombocytopenia, anemia, febrile neutropenia, white blood cell count decreased, lymphocyte count decreased, sepsis, hypokalemia, pancreatitis, transaminase increased, activated partial thromboplastin time prolonged, decreased appetite, dehydration, and nausea.

Serious adverse reactions occurred in 59% of patients. The most common serious adverse reactions (in ≥ 3% of patients) were febrile neutropenia, pyrexia, sepsis, dehydration, pancreatitis, acute kidney injury, bacteremia, decreased appetite, dysarthria, enterocolitis infectious, hypotension, muscular weakness, stomatitis, vomiting, and weight decreased.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received RYLAZE. Adverse reactions resulting in permanent discontinuation included pancreatitis (8%) and hypersensitivity (2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3: Non-hematologic Adverse Reactions (≥ 5% incidence) in Patients Receiving RYLAZE as a Component of Multi-Agent Chemotherapy (Study JZP458-201)[a]

System Organ Class	Adverse Reaction	RYLAZE (Intramuscular 25/25/50 mg/m^2) N=51	
		All grades	Grade ≥ 3
Blood and lymphatic system disorders	Febrile neutropenia	14 (28)	14 (28)
Cardiac disorders	Sinus tachycardia	8 (16)	1 (2)
Gastrointestinal disorders	Nausea	18 (35)	3 (6)
	Vomiting	17 (33)	2 (4)
	Stomatitis	14 (28)	2 (4)
	Abdominal pain*	13 (26)	1 (2)
	Diarrhea	12 (24)	1 (2)
	Constipation	7 (14)	1 (2)
	Pancreatitis*	6 (12)	4 (8)
	Gastritis	3 (6)	1 (2)
	Gastroesophageal reflux disease	3 (6)	0
General disorders and administration site conditions	Fatigue*	11 (22)	0
	Pyrexia	10 (20)	0
	Injection site reaction	4 (8)	0
	Gait disturbance	3 (6)	0
Infections and infestations	Sepsis	5 (10)	5 (10)

System Organ Class	Adverse Reaction	RYLAZE (Intramuscular 25/25/50 mg/m^2) N=51	
		All grades	Grade ≥ 3
Injury, poisoning and procedural complications	Contusion	7 (14)	0
Investigations	Transaminase increased*	11 (22)	4 (8)
	Weight decreased	7 (14)	2 (4)
	Blood bilirubin increased*	4 (8)	2 (4)
	Activated partial thromboplastin time prolonged	3 (6)	3 (6)
	Antithrombin III decreased	3 (6)	0
	Blood creatinine increased	3 (6)	0
Metabolism and nutrition disorders	Decreased appetite	14 (28)	3 (6)
	Hypokalemia	11 (22)	4 (8)
	Dehydration	6 (12)	3 (6)
	Hyperglycemia	6 (12)	2 (4)
	Hypertriglyceridemia	6 (12)	1 (2)
	Hypocalcemia	4 (8)	1 (2)
	Hypoalbuminemia	3 (6)	0
	Hyponatremia	3 (6)	0
Musculoskeletal and connective tissue disorders	Pain in extremity	8 (16)	1 (2)
	Back pain	6 (12)	1 (2)
	Arthralgia	3 (6)	0
	Muscular weakness	3 (6)	1 (2)
Nervous system disorders	Headache	11 (22)	0
	Dizziness	4 (8)	0

System Organ Class	Adverse Reaction	RYLAZE (Intramuscular 25/25/50 mg/m^2) N=51	
		All grades	Grade ≥ 3
	Paresthesia	4 (8)	0
Psychiatric disorders	Anxiety	5 (10)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	Cough	7 (14)	0
	Epistaxis	5 (10)	2 (4)
	Oropharyngeal pain	5 (10)	0
	Nasal congestion	4 (8)	0
	Rhinorrhea	4 (8)	0
Skin and subcutaneous tissue disorders	Dry skin	5 (10)	0
	Rash	4 (8)	0
	Drug eruption	3 (6)	0
	Pruritus	3 (6)	0
	Skin hyperpigmentation	3 (6)	0
Vascular disorders	Hypertension	7 (14)	0
	Hypotension	4 (8)	2 (4)

Grading is based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

[a] Hematologic adverse reactions are not included in the table. Patients received RYLAZE as a component of various multi-agent chemotherapy regimens in an uncontrolled trial making causality unclear.

[b] RYLAZE was administered intramuscularly at a dosage of 25 mg/m^2 on Monday and Wednesday and 50 mg/m^2 on Friday. RYLAZE was administered as a component of multi-agent chemotherapy.

[c] The analysis data cut-off date was 19th July, 2021.

*Adverse drug reaction 'Abdominal pain' is a combined term of 'Abdominal pain' and 'Abdominal pain upper'; 'Bilirubin increased' is a combined term of 'Blood bilirubin increased' and 'Bilirubin conjugated increased'; 'Fatigue' is a combined term of 'Fatigue' and 'Asthenia'; 'Pancreatitis' is a combined term of 'Pancreatitis' and 'Pancreatitis acute'; 'Transaminase increased' is a combined term of 'Transaminase increased', 'Alanine aminotransferase increased' and 'Aspartate aminotransferase increased'.

8.3 Less Common Clinical Trial Adverse Reactions

Less common adverse drug reactions that occurred in the JZP458-201 Study (N=167) treated with RYLAZE included:

Immune: anaphylactic reaction, drug hypersensitivity

Investigations: blood fibrinogen decreased

Metabolism and nutrition: hyperammonaemia

Nervous system: superior sagittal sinus thrombosis

Respiratory, thoracic and mediastinal: pulmonary embolism

8.5 Post-Market Adverse Reactions

Not available.

9 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with RYLAZE.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

RYLAZE catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia. The mechanism of action of RYLAZE is based on the killing of leukemic cells due to depletion of plasma asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize asparagine, and therefore depend on an exogenous source of asparagine for survival.

10.2 Pharmacodynamics

RYLAZE exposure-response relationships and the time course of pharmacodynamic response are unknown.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of RYLAZE were determined based on serum asparaginase activity (SAA).

Sparse PK SAA samples were collected from patients with ALL/LBL who developed hypersensitivity or silent inactivation to long-acting *E. coli*-derived asparaginases, and a population PK approach was used to characterize the PK of RYLAZE. Patients received 6 doses of RYLAZE at 3 different dosages, including the recommended dosage, 25 mg/m^2 administered intramuscularly on Monday and Wednesday and 50 mg/m^2 on Friday, as a replacement for each dose of pegaspargase remaining on their original treatment plan [see 14 CLINICAL TRIALS].

Table 4 summarizes the PK parameters from the population PK analysis in the target patient population.

Table 4: Summary of RYLAZE Pharmacokinetic Parameters based on SAA in Patients in Study JZP458-201

	C_{max} (IU/mL)	T_{max} (h) [a]	$t_{1/2}$ (h)	AUC_{0-336} (h. IU/mL)	CL/F (L/h) [b]	V/F (L) [b]
Arithmetic Mean (%CV) 25/25/50 mg/m^2 (M/W/F) Intramuscular (N=50)	3.29 (49.2)	13.7 (4.67 – 23.6)	19.1 (3.97)	456 (49.9)	0.5 (87.4)	2.16 (93.6)

[a] T_{max} reported as median and range.

[b] CL/F: apparent clearance; V/F: apparent volume of distribution.

Absorption:

The median T_{max} of RYLAZE is 13.7 hours. The mean absolute bioavailability for IM administration is 37% in healthy subjects. The maximum SAA (C_{max}) and area under the SAA-time curve (AUC) increase proportionally over a dosage range from 12.5 to 50 mg/m^2.

Distribution:

The mean (%CV) apparent volume of distribution of RYLAZE is 2.16 (93.6) L.

Metabolism:

RYLAZE is expected to be metabolized into small peptides by catabolic pathways.

Elimination:

The mean (%CV) apparent clearance of RYLAZE is 0.5 (87.4) L/hour and the apparent half-life following intramuscular administration is 19.1 hours (3.97).

Special Populations and Conditions:

No study has been conducted to evaluate the impact of renal and hepatic impairment on the pharmacokinetics of RYLAZE.

11 STORAGE, STABILITY AND DISPOSAL

Store RYLAZE refrigerated at 2°C to 8°C in the original carton to protect from light. Do not shake or freeze product. Discard unused product in accordance with local requirements. Do not use beyond expiration date printed on the carton or vial.

In-use storage period: administer within 4 hours of preparing syringe(s). The syringe(s) should be stored at room temperature and does not need to be protected from light before use.

12 SPECIAL HANDLING INSTRUCTIONS

RYLAZE is a clear to opalescent, colourless to slightly yellow sterile solution. Visually inspect parenteral drug products for particulate matter, cloudiness, or discolouration prior to administration. If any of these are present, discard the vial. RYLAZE does not contain a preservative.

If partial vial is used, do not save, or reuse the unused drug for later administration. Discard unused product.

Protect from light. Do not shake or freeze the product [see 11 STORAGE, STABILITY AND DISPOSAL].

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: crisantaspase recombinant

Chemical name: L-asparaginase

Molecular formula and molecular mass: crisantaspase recombinant is a non-disulfide bonded, tetrameric crisantaspase (L-asparaginase) enzyme consisting of 4 identical polypeptide subunits with a combined molecular weight of 140 kDa; each individual subunit has a molecular weight of 35 kDa.

Table 5: Physicochemical properties

Property	Detail
Description	Colourless to slightly yellow solution, clear to opalescent liquid
Activity	550-850 units per mg protein
pH	7.0 ± 0.5
Molecular weight	140 kDa Tetramer; each individual subunit has a molecular weight of 35 kDa
Concentration	18.0-22.0 mg/mL

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6: Summary of patient demographics for clinical trials in in adults and pediatric patients with ALL or LBL who developed hypersensitivity to *E. coli*-derived asparaginases.

Study #	Study design	Dosage, route of administration and duration	Study participants (n)	Mean age (Range)	Sex
JZP458-201	An open-label, multi-cohort, multicenter, safety and clinical pharmacology trial in adults and pediatric patients with ALL or LBL who had developed hypersensitivity to *E. coli*-derived asparaginase.	**Cohort 1a:** RYLAZE 25 mg/m^2 administered intramuscularly on a Monday, Wednesday, and Friday schedule. * **Cohort 1b:** RYLAZE 37.5 mg/m^2 administered intramuscularly on a Monday, Wednesday, and Friday schedule. * **Cohort 1c:** RYLAZE 25 mg/m^2 administered intramuscularly on Monday and Wednesday and 50 mg/m^2 on Friday. *	137 Cohort 1a: N=33 Cohort 1b: N=53 Cohort 1c: N=51	10 years (1 to 25 years)	Male: 59% Female: 41%

*Over two weeks (total of 6 doses) to replace each scheduled dose of pegaspargase.

14.2 Study Results

The safety and efficacy of RYLAZE was assessed in study JZP458-201, a Phase 2/3, open-label, multicenter trial in adult and pediatric patients with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) who had developed hypersensitivity to E. coli-derived asparaginase. Patients received RYLAZE at various dosages administered intramuscularly every Monday, Wednesday, and Friday for a total of 6 doses to replace each planned dose of pegaspargase.

In the ongoing study JZP458-201, 137 patients received at least one dose of RYLAZE. The median age was 10 years (range, 1 to 25 years); 59% were male, 41% were female, 69% were white, 13% were Black/African American, 4% were Asian and 10% were other or unknown race. A total of 34% were Hispanic or Latino. One hundred nineteen (87%) patients had experienced

a hypersensitivity reaction to pegaspargase, 7 patients (5%) reported silent inactivation and 11 (8%) patients had experienced an allergic reaction with inactivation.

The determination of efficacy was based on a demonstration of the achievement and maintenance of nadir serum asparaginase activity (NSAA) above the level of 0.1 U/mL.

The results of modelling and simulations showed that for a dosage of 25 mg/m^2 administered intramuscularly (IM) on a Monday and Wednesday and 50 mg/m^2 administered IM on a Friday, the proportion of patients expected to maintain NSAA ≥ 0.1 U/mL was 93.0% (95% CI: 91.8%, 94.1%) at 48 hours after a dose of RYLAZE, and 91.0% (95% CI: 89.7%, 92.2%) at 72 hours after a dose of RYLAZE.

14.4 Immunogenicity

The incidence of ADA and subsequent effects on pharmacokinetics, pharmacodynamics, safety, or effectiveness have not been established.

As with all L-asparaginase class products, there is a potential for immunogenicity with RYLAZE.

16 NON-CLINICAL TOXICOLOGY

Repeated dose toxicity

In a GLP-compliant study, RYLAZE was administered IV once daily to groups of rats (n=10/sex/group) for up to 14 days at doses of 0, 4.6, 15.2, and 45.6 mg/kg (0, 27.6, 91.2, and 273.6 mg/m^2, respectively). Recovery animals (n=5/sex/group) were included in the control and high dose groups. At the highest dose (273.6 mg/m^2), significant clinical observations on Day 6 required interruption of dosing and initiation of the 2-week recovery or euthanasia. Hematology changes indicative of decreased hematopoiesis, increased glycemia and blood urea nitrogen, and decreased serum protein and liver enzymes were noted. Microscopic findings of decreased cellularity in the femoral bone marrow, decreased splenic red pulp, extramedullary hematopoiesis, decreased lymphocytes in the thymus and the spleen, and secretory depletion in the pancreas were also reported. Observations in the recovery animals (control and high dose) suggested these findings were reversible. At lower doses (≤ 91.2 mg/m^2), dose-related effects as described above were also observed but were lower in magnitude, incidence, or severity and not considered adverse. The no-observed-adverse-effect level (NOAEL) was determined to be 91.2 mg/m^2, which provided exposure multiples of 24- and 10-fold based on the anticipated human C_{max} and $AUC_{0\text{-}336h}$ at the proposed human dose of IM 25/25/50 mg/m^2 MWF. The incidence of ADA induction to RYLAZE was 0% (0/30 animals) in the control group, 45% (9/20) at 27.6 mg/m^2, 5% (1/20) at 91.2 mg/m^2, and 20% (6/30, all from the recovery animals) at 273.6 mg/m^2.

Genotoxicity and carcinogenicity studies

No studies have been performed to evaluate the mutagenicity or carcinogenicity of RYLAZE.

Reproductive and developmental toxicity studies

No studies have been performed to evaluate the potential reproductive and developmental toxicity of RYLAZE. RYLAZE mechanism of action is to catalyze the conversion of asparagine to aspartic acid and ammonia thereby resulting in profound depletion of circulating asparagine levels. Studies demonstrating the requirement for asparagine during normal pregnancy and fetal development in animals have been previously published, along with reports of abortion, stunted growth, malformations, and developmental delays effects of asparagine depletion in pregnant and nursing animals and their offspring when exposed to *E. coli*-derived and *Erwinia*-derived asparaginases.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr RYLAZE™
crisantaspase recombinant solution

Read this carefully before you start taking **RYLAZE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RYLAZE**.

What is RYLAZE used for?

RYLAZE is used to treat acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) in adults and pediatric patients 1 year of age and older where a reduction in a substance called asparagine may be useful. Most commonly it is used when patients have had a severe hypersensitivity reaction to similar medicines and, therefore, had to stop using them.

How does RYLAZE work?

RYLAZE contains an enzyme asparaginase that breaks down asparagine, an important component for cell survival. Unlike normal cells, cancer cells are unable to make their own asparagine, which is required for DNA synthesis and cell survival. Therefore, the depletion of asparagine by asparaginase kills cancer cells, while healthy cells are not affected.

What are the ingredients in RYLAZE?

Medicinal ingredient:

crisantaspase recombinant

Non-medicinal ingredients:

- polysorbate 80
- sodium chloride
- sodium hydroxide
- sodium phosphate dibasic anhydrous
- sodium phosphate monobasic monohydrate
- trehalose dihydrate

RYLAZE comes in the following dosage forms:

Solution for Injection: 10 mg/0.5 mL in a single-dose vial.

Do not use RYLAZE if you:

- are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient.
- have ever had serious pancreatitis during previous asparaginase therapy.
- have ever had blood clots during previous asparaginase therapy.
- have ever had serious bleeding during previous asparaginase therapy.
- have ever had serious allergic reaction to *Erwinia asparaginase*, including anaphylaxis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RYLAZE. Talk about any health conditions or problems you may have, including if you:

- have had serious allergic reactions to *Erwinia asparaginase*, including anaphylaxis. Your doctor may pause or stop treatment with RYLAZE, if any allergic reactions occur.
- currently have or had pancreatitis. RYLAZE can cause pancreatitis, which may become life-threatening or lead to other problems. In case of severe pancreatitis, your doctor may stop the treatment with RYLAZE. In the case of mild pancreatitis, your doctor may withhold RYLAZE until the signs and symptoms subside. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.
- have or had diabetes mellitus or high blood sugar. RYLAZE can cause high blood sugar levels, which may need to be treated. RYLAZE may have to be stopped until the blood sugar is lowered. Your doctor will monitor your glucose levels during treatment.
- suffer from bleeding and blood clot disorders. During treatment your body's ability to prevent excessive bleeding may be affected. In the case you experience any significant bleeding your treatment will be stopped. Your doctor will determine if, and when, treatment can be restarted.

Other warnings you should know about:

- If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. RYLAZE can cause embryonic and fetal harm when given to a pregnant woman.
- It is unknown whether RYLAZE is present in human breast milk. Therefore, RYLAZE must not be used during breast-feeding due to the risk to a breast-feeding child. Ask your doctor about when breast-feeding can resume after your last dose of RYLAZE.
- In males, potential for a decrease in sperm count cannot be ruled out. Talk to your healthcare professional if you have questions about this.
- If you are sexually mature you must use contraceptives or remain abstinent during treatment with RYLAZE and for 3 months after the end of treatment. Since an indirect interaction between components of oral contraceptives and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe. Ask your healthcare professional for advice on the best contraceptive method that you can use.
- Do not drive or use machines when taking this medicine because it may make you feel drowsy, tired, or confused.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take RYLAZE:

RYLAZE is given by injection into a muscle (intramuscular injection). This product should be administered by your healthcare professional in a hospital setting where appropriate resuscitation equipment is available.

Usual dose:

Your healthcare professional will determine the dose of RYLAZE you will receive. The dose you receive will be based on your age, and body surface area or body weight.

The recommended dosage of RYLAZE is 25 mg/m^2 on Monday and Wednesday and 50 mg/m^2 on Friday, administered intramuscularly, for a total of six doses for each treatment course.

Overdose:

If you think you, or a person you are caring for, have taken too much **RYLAZE,** contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your scheduled treatment, contact your healthcare professional as soon as possible to schedule your next treatment.

What are possible side effects from using RYLAZE?

These are not all the possible side effects you may have when taking RYLAZE. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects were observed in patients receiving RYLAZE: fatigue, decreased appetite, nausea, headache, pain in extremity, increased blood pressure, decrease in weight, increased heart rate, constipation, mouth sores, dehydration, back pain, anxiety, cough, pain in mouth or throat, and dry skin.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Abdominal pain		✓	
Vomiting	✓		
Abnormal liver function values		✓	
Diarrhea	✓		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Abnormal laboratory values including decreased potassium or increased triglycerides		✓	
Increased blood sugar levels		✓	
Fever		✓	✓
Infection, including in the blood: fever, increased heart rate, rapid breathing		✓	
Allergic reactions: rash, itching, swelling, shortness of breath, injection site reaction		✓	✓
Bleeding: bleeding from gums, nose or other sites, abnormal bruising	✓		✓
COMMON			
Inflammation of the pancreas: Pain in the upper abdomen, nausea, vomiting (pancreatitis)		✓	✓
Severe allergic reaction that may cause loss of consciousness, difficulty in breathing, decreased blood pressure, and could be life-threatening (anaphylactic shock)		✓	✓
Blood clot, including in the lung or brain: chest pain, shortness of breath, blurred vision, loss of consciousness, or pain/numbness/spasm in other parts of body		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store RYLAZE refrigerated at 2°C to 8°C in the original carton to protect from light. Do not shake or freeze product.

Keep out of reach and sight of children.

If you want more information about RYLAZE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.jazzpharma.com, or by calling 1-800-520-5568.

This leaflet was prepared by: Jazz Pharmaceuticals Ireland Limited.

Imported by: Jazz Pharmaceuticals Canada Inc.
4080 Confederation Parkway, Suite 602
Mississauga, Ontario L5B 0G1

Last Revised: SEP 02, 2022