

RYLAZE- asparaginase erwinia chrysanthemi (recombinant)-rywn injection **Jazz Pharmaceuticals, Inc.**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RYLAZE safely and effectively. See full prescribing information for RYLAZE.

RYLAZE® (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection, for intramuscular use
Initial U.S. Approval: 2021

RECENT MAJOR CHANGES

Dosage and Administration (2.1, 2.2, 2.4) 11/2022
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5) 11/2022

INDICATIONS AND USAGE

RYLAZE is an asparagine specific enzyme 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 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase. (1)

DOSAGE AND ADMINISTRATION

There are two RYLAZE regimens that can be used to replace a long-acting asparaginase product. The recommended dosages of RYLAZE are:

When administered every 48 hours

- 25 mg/m² intramuscularly every 48 hours;

When administered Monday/Wednesday/Friday

- 25 mg/m² intramuscularly on Monday morning and Wednesday morning and 50 mg/m² intramuscularly on Friday afternoon. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/0.5 mL solution in a single-dose vial. (3)

CONTRAINDICATIONS

RYLAZE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to RYLAZE, including anaphylaxis. (4)
- Serious pancreatitis during previous L-asparaginase therapy. (4)
- Serious thrombosis during previous L-asparaginase therapy. (4)
- Serious hemorrhagic events during previous L-asparaginase therapy. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity: Monitor for signs or symptoms. Discontinue RYLAZE for serious reaction. (5.1)
- Pancreatitis: Monitor for symptoms. Discontinue if pancreatitis occurs. (5.2)
- Thrombosis: Discontinue RYLAZE for severe or life-threatening thrombosis. Provide anticoagulation therapy as indicated. (5.3)
- Hemorrhage: Discontinue RYLAZE for severe or life-threatening hemorrhage. (5.4)
- Hepatotoxicity: Discontinue RYLAZE for grade 4 increases of bilirubin. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence > 20%) are abnormal liver test, nausea, musculoskeletal pain, infection, fatigue, headache, febrile neutropenia, pyrexia, hemorrhage, stomatitis, abdominal pain, decreased appetite, drug hypersensitivity, hyperglycemia, diarrhea, pancreatitis, and hypokalemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals Ireland Limited at 1-800-520-5568 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RYLAZE 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 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

There are two RYLAZE regimens that can be used to replace a long-acting asparaginase product. The recommended dosages of RYLAZE are:

When administered every 48 hours:

- 25 mg/m² administered intramuscularly every 48 hours;

When administered on a Monday/Wednesday/Friday schedule:

- 25 mg/m² intramuscularly on Monday morning and Wednesday morning, and 50 mg/m² intramuscularly on Friday afternoon. Administer the Friday afternoon dose 53 to 58 hours after the Wednesday morning dose (e.g., 8:00 am on Monday and Wednesday, and 1:00 pm to 6:00 pm on Friday) [see *Clinical Pharmacology (12.3)*, *Clinical Studies (14)*].

Table 1 shows the number of RYLAZE dosages recommended for the intended duration of treatment for replacement of one dose of calaspargase pegol products (3 weeks of asparaginase coverage) or one dose of pegaspargase products (2 weeks of asparaginase coverage). See the full prescribing information for the long-acting asparaginase product to determine the total duration of administration of RYLAZE as replacement therapy.

Table 1: Recommended Duration of RYLAZE Dosing to Replace One Long-Acting Asparaginase Dose

When RYLAZE is Administered:	Recommended Duration of RYLAZE to Replace Calaspargase Pegol Products	Recommended Duration of RYLAZE to Replace Pegaspargase Products
25 mg/m ² intramuscular every 48 hours	Replace one dose of calaspargase pegol products with 11 doses of RYLAZE	Replace one dose of pegaspargase products with 7 doses of RYLAZE
25 mg/m ² intramuscular on Monday morning and Wednesday morning, and 50 mg/m ² intramuscular on Friday afternoon*	Replace one dose of calaspargase pegol products with 9 doses of RYLAZE	Replace one dose of pegaspargase products with 6 doses of RYLAZE

*See bullet above for timing of 25/25/50 mg/m² dosing of RYLAZE.

2.2 Recommended Premedication

Premedicate patients with acetaminophen, an H-1 receptor blocker (such as diphenhydramine), and an H-2 receptor blocker (such as famotidine) 30-60 minutes prior to administration of RYLAZE to decrease the risk and severity of hypersensitivity reactions [see *Warnings and Precautions (5.1)*].

2.3 Recommended Monitoring and Dosage Modifications for Adverse Reactions

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

Table 2: Dosage Modifications

Adverse Reaction	Severity*	Action
Hypersensitivity Reaction <i>[see Warnings and Precautions (5.1)]</i>	Grade 2	<ul style="list-style-type: none"> Treat the symptoms.
	Grade 3 to 4	<ul style="list-style-type: none"> Discontinue RYLAZE permanently.
Pancreatitis <i>[see Warnings and Precautions (5.2)]</i>	Grade 2 to 4	<ul style="list-style-type: none"> 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 <i>[see Warnings and Precautions (5.3)]</i>	Uncomplicated thrombosis	<ul style="list-style-type: none"> Hold RYLAZE. Treat with appropriate antithrombotic therapy. Upon resolution of symptoms, consider resuming RYLAZE, while continuing antithrombotic therapy.
	Severe or life-threatening thrombosis	<ul style="list-style-type: none"> Discontinue RYLAZE permanently. Treat with appropriate antithrombotic therapy.
Hemorrhage <i>[see Warnings and Precautions (5.3)]</i>	Grade 3 to 4	

<i>and Precautions (5.4)]</i>		<ul style="list-style-type: none"> • Hold RYLAZE. • Evaluate for coagulopathy and consider clotting factor replacement as needed. • Resume RYLAZE with the next scheduled dose if bleeding is controlled.
Hepatotoxicity [see Warnings and Precautions (5.5)]	Total bilirubin > 3 times to ≤ 10 times the ULN	<ul style="list-style-type: none"> • Hold RYLAZE until total bilirubin levels decrease to ≤ 1.5 times the ULN.
	Total bilirubin > 10 times the ULN	<ul style="list-style-type: none"> • Discontinue RYLAZE and do not make up missed doses.

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

** Upper limit of normal

2.4 Preparation and Administration Instructions

Ensure that medical support is available to appropriately manage anaphylactic reactions when administering RYLAZE [see Warnings and Precautions (5.1)].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter, cloudiness, or discoloration are present, discard the vial.

- Use aseptic technique.
- Determine the dose, total volume of RYLAZE solution required, and the number of RYLAZE vials needed based on the individual patient's BSA. More than one vial may be needed for a full dose.
- Withdraw the indicated injection volume of RYLAZE into the syringe for injection.
 - o Do not shake the vial.
 - o Limit the volume of RYLAZE at a single injection site to 2 mL.
 - o If the volume to be administered is greater than 2 mL, divide the doses equally into multiple syringes, one for each injection site.
 - o Discard the remaining unused RYLAZE in the single-dose vial.
- Administer RYLAZE by intramuscular injection.
 - o Rotate injection sites.
 - o Do not inject RYLAZE into scar tissue or areas that are reddened, inflamed, or swollen.
- If the prepared dose is not used immediately, store the syringe(s) at room temperature 15°C to 25°C (59°F to 77°F) for up to 8 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours. The syringe does not need to be protected from light during storage.

3 DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/0.5 mL clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

RYLAZE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis [see *Warnings and Precautions (5.1)*];
- Serious pancreatitis during previous asparaginase therapy [see *Warnings and Precautions (5.2)*];
- Serious thrombosis during previous asparaginase therapy [see *Warnings and Precautions (5.3)*];
- Serious hemorrhagic events during previous asparaginase therapy [see *Warnings and Precautions (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions after the use of RYLAZE occurred in 29% of patients in clinical trials, and it was severe in 6% of patients [see *Adverse Reactions (6.1)*]. Anaphylaxis was observed in 2% of patients after intramuscular administration. Discontinuation of RYLAZE due to hypersensitivity reactions occurred in 5% of patients. Hypersensitivity reactions were higher in patients who received intravenous asparaginase erwinia chrysanthemi (recombinant)-rywn. The intravenous route of administration is not approved.

In patients administered RYLAZE intramuscularly in clinical trials, the median number of doses of RYLAZE that patients received prior to the onset of the first hypersensitivity reaction was 12 doses (range: 1-64 doses). The most commonly observed reaction was rash (19%), and 1 patient (1%) experienced a severe rash.

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.

Premedicate patients prior to administration of RYLAZE as recommended [see *Dosage and Administration (2.2)*]. Because of the risk of serious allergic reactions (e.g., life-threatening anaphylaxis), administer RYLAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, oxygen, intravenous steroids, antihistamines) [see *Dosage and Administration (2.3)*]. Discontinue RYLAZE in patients with serious hypersensitivity reactions [see *Dosage and Administration (2.3)*].

5.2 Pancreatitis

Pancreatitis, including elevated amylase or lipase, was reported in 20% of patients in clinical trials of RYLAZE and was severe in 8% [see *Adverse Reactions (6.1)*].

Symptomatic pancreatitis occurred in 7% of patients, and it was severe in 6% of patients. Elevated amylase or lipase without symptomatic pancreatitis was observed in 13% of patients treated with RYLAZE. Hemorrhagic or necrotizing pancreatitis have been reported with L-asparaginase class products.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Assess serum amylase and lipase levels in patients with any signs or symptoms of pancreatitis. 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 1.5 times the ULN [see *Dosage and Administration (2.3)*]. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.

5.3 Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis and pulmonary embolism, have been reported in 1% of patients following treatment with RYLAZE. 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 *Dosage and Administration (2.3)*].

5.4 Hemorrhage

Bleeding was reported in 25% of patients treated with RYLAZE, and it was severe in 2%. Most commonly observed reactions were bruising (12%) and nose bleed (9%) [see *Adverse Reactions (6.1)*].

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 *Dosage and Administration (2.3)*].

5.5 Hepatotoxicity

Elevated bilirubin and/or transaminases occurred in 75% of patients treated with RYLAZE in clinical trials, and 26% had Grade ≥ 3 elevations. Elevated bilirubin occurred in 28% of patients treated with RYLAZE in clinical trials, and 2% had Grade ≥ 3 elevations. Elevated transaminases occurred in 73% of patients treated with RYLAZE in clinical trials, and 25% had Grade ≥ 3 elevations [see *Adverse Reactions (6.1)*].

Inform patients of the signs and symptoms of hepatotoxicity. 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 *Dosage and Administration (2.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in other sections of the labeling:

- Hypersensitivity Reactions [see *Warnings and Precautions (5.1)*]
- Pancreatic Toxicity [see *Warnings and Precautions (5.2)*]

- Thrombosis [see Warnings and Precautions (5.3)]
- Hemorrhage [see Warnings and Precautions (5.4)]
- Hepatotoxicity [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RYLAZE described in the WARNINGS AND PRECAUTIONS reflect exposure in 167 patients administered RYLAZE intramuscularly at various dosages when used in combination with chemotherapy in study JZP458-201 [see *Clinical Studies (14)*]. These patients received a median of 4 courses of RYLAZE (range: 1-15 courses); 65% of patients received at least four courses.

The safety of RYLAZE described below and in Table 3 was evaluated in study JZP458-201, a multi-cohort study. Patients received RYLAZE administered intramuscularly at dosages of 25 mg/m² on Monday, Wednesday, and Friday or 25 mg/m² on Monday and Wednesday, and 50 mg/m² on Friday, for 6 doses as a replacement for a single dose of pegaspargase as a component of multi-agent chemotherapy [see *Clinical Studies (14)*]. The patients had a median age of 11 years (range: 1-25 years); the majority of patients were male (57%) and White (68%). The patients received a median of 4 courses of RYLAZE (range: 1-14 courses); 65% of patients received at least four courses.

A fatal adverse reaction (infection) occurred in 1 patient treated with the RYLAZE 25/25/25 mg/m² dosage. Serious adverse reactions occurred in 60% of patients who received the recommended dosages of RYLAZE. The most frequent nonhematological serious adverse reactions (in ≥ 5% of patients) were febrile neutropenia, infection, drug hypersensitivity, pyrexia, nausea, dehydration, stomatitis, acute kidney injury, pancreatitis, diarrhea, and viral infection. Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received RYLAZE intramuscularly at the recommended dosages. Adverse reactions resulting in permanent discontinuation included pancreatitis (5%), drug hypersensitivity (4%), and infection (1%).

All patients treated with the recommended dosages of RYLAZE as a component of multi-agent chemotherapy experienced neutropenia, anemia, or thrombocytopenia. The most common nonhematological adverse reactions (incidence > 20%) in patients were abnormal liver test, nausea, musculoskeletal pain, infection, fatigue, headache, febrile neutropenia, pyrexia, hemorrhage, stomatitis, abdominal pain, decreased appetite, drug hypersensitivity, hyperglycemia, diarrhea, pancreatitis, and hypokalemia. Table 3 shows the common adverse reactions occurring in at least 15% of the patients.

Table 3: Adverse Reactions (≥ 15% Incidence) in Patients Receiving RYLAZE as a Component of Multi-Agent Chemotherapy in Study JZP458-201

Adverse Reaction	RYLAZE 25/25/25 mg/m ² Intramuscular Dosage ^a (N = 33)		RYLAZE 25/25/50 mg/m ² Intramuscular Dosage ^a (N = 51)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)

Abnormal liver test* [#]	70	18	75	27
Musculoskeletal pain*	45	6	35	4
Nausea*	45	9	47	8
Fatigue*	36	18	22	18
Headache	36	0	22	0
Infection* ^b	36	15	27	17
Febrile neutropenia	30	30	27	27
Pyrexia	30	6	20	0
Hemorrhage*	24	0	27	6
Stomatitis	24	12	27	4
Abdominal pain*	21	0	25	2
Decreased appetite	21	6	27	6
Drug hypersensitivity*	21	6	24	2
Hyperglycemia	21	3	12	4
Diarrhea*	18	6	25	4
Tachycardia*	18	0	16	2
Cough	15	0	14	0
Dehydration	15	9	12	6
Insomnia	15	0	4	0
Peripheral neuropathy*	15	0	6	0
Pancreatitis* [#]	12	0	22	10
Hypokalemia	9	3	22	8

* Includes grouped terms: **Abnormal liver test:** alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, transaminases increased; **Musculoskeletal pain:** arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, pain in extremity; **Nausea:** nausea, vomiting; **Fatigue:** fatigue, asthenia; **Infection:** sepsis, upper respiratory tract infection, enterocolitis infectious, skin infection, bacteremia, paronychia, pneumonia, otitis externa, soft tissue infection, abdominal infection, conjunctivitis, device related infection, folliculitis, lymph gland infection, necrotizing fasciitis, perirectal abscess, peritonsillar abscess, sinusitis, subcutaneous abscess, wound infection; **Drug hypersensitivity:** drug hypersensitivity, rash, infusion related reaction, lip swelling, periorbital edema, throat irritation, urticaria, dry skin, eczema, erythema, hand dermatitis, rash maculo-papular, rash papular; **Hemorrhage:** contusion, epistaxis, catheter site hemorrhage, petechiae, hematochezia, menorrhagia, mouth hemorrhage, increased tendency to bruise, rectal hemorrhage; **Abdominal pain:** abdominal pain, abdominal pain upper; **Diarrhea:** diarrhea, colitis; **Tachycardia:** sinus tachycardia, tachycardia; **Peripheral neuropathy:** peripheral motor neuropathy, neuropathy peripheral, peripheral sensory neuropathy; **Pancreatitis:** pancreatitis, pancreatitis acute, amylase increased, lipase increased.

*Includes adverse event terms and laboratory abnormalities

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

^a RYLAZE was administered as a component of multi-agent chemotherapy regimens on a Monday, Wednesday, and Friday schedule.

^b Does not include the following fatal adverse reactions: infection (N=1).

Clinically relevant adverse reactions in < 15% of patients who received RYLAZE in combination with chemotherapy included:

Gastrointestinal disorders: Abdominal discomfort, abdominal distension, constipation, gastritis

General disorders and administration site conditions: Infusion site reaction, injection site reaction, pain

Infections and infestations: Viral infection, bacterial infection, fungal infection

Investigations: Antithrombin III decreased, blood cholesterol increased, blood fibrinogen decreased, activated partial thromboplastin time prolonged

Metabolism and nutrition disorders: Acidosis, hyperammonemia, hyperphosphatemia, hypertriglyceridemia, hypoglycemia

Musculoskeletal and connective tissue disorders: Bone pain, muscular weakness, muscle spasms

Nervous system disorders: Paresthesia, dizziness, gait disturbance, hyperammonemic encephalopathy

Psychiatric disorders: Agitation, anxiety, irritability

Respiratory, thoracic, and mediastinal disorders: Acute respiratory distress syndrome, pulmonary edema

Renal and urinary disorders: Acute kidney injury

Skin and subcutaneous disorders: Pruritus

Vascular disorders: Hypertension, hypotension, thrombosis

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies, RYLAZE can cause fetal harm when administered to a pregnant woman. There are no available data on RYLAZE use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive and developmental toxicity studies, intramuscular administration of asparaginase *Erwinia chrysanthemi* to pregnant rats and rabbits during organogenesis resulted in structural abnormalities and embryo-fetal mortality (see *Data*) at exposures below those in patients at the recommended human dose. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Animal reproductive and developmental toxicity studies have not been conducted with

RYLAZE.

In embryofetal development studies, asparaginase *Erwinia chrysanthemi* was administered intramuscularly every other day during the period of organogenesis to pregnant rats (at 3, 6, or 12 mg/m²) and rabbits (at 0.12, 0.30, or 0.48 mg/m²). In rats given 12 mg/m² (approximately 0.48 times the maximum recommended human dose), maternal toxicity of decreased body weight gain was observed, as was a fetal finding of increased incidence of partially undescended thymic tissue. In rabbits, maternal toxicity consisting of decreased body weight was observed at 0.48 mg/m² (approximately 0.02 times the maximum recommended human dose). Increased post-implantation loss, a decrease in the number of live fetuses, and gross abnormalities (e.g., absent kidney, absent accessory lung lobe, additional subclavian artery, and delayed ossification) were observed at doses of ≥ 0.12 mg/m² (approximately 0.005 times the maximum recommended human dose).

8.2 Lactation

Risk Summary

There are no data on the presence of asparaginase *erwinia chrysanthemi* (recombinant)-rywn in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for adverse reactions in the breastfed child, advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

RYLAZE can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Pregnancy Testing

Pregnancy testing is recommended in females of reproductive potential prior to initiating RYLAZE.

Contraception

Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with RYLAZE and for 3 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of RYLAZE in the treatment of ALL and LBL have been established in pediatric patients 1 month to < 17 years who have developed hypersensitivity to a long-acting *E. coli*-derived asparaginase. Use of RYLAZE in these age groups is supported by evidence from an adequate and well-controlled study in adults and pediatric patients. The trial included 139 pediatric patients, including 2 infants (1 month to < 2 years), 99 children (2 years to < 12 years old), and 38 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 month of age.

8.5 Geriatric Use

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.

11 DESCRIPTION

Asparaginase erwinia chrysanthemi (recombinant)-rywn contains an asparagine specific bacterial enzyme (L-asparaginase). L-asparaginase is a tetrameric enzyme that consists of four identical 35 kDa subunits with a combined molecular weight of 140 kDa. The amino acid sequence is identical to native asparaginase *Erwinia chrysanthemi* (also known as crisantaspase). The activity of asparaginase erwinia chrysanthemi (recombinant)-rywn is expressed in units, defined as the amount of enzyme that catalyzes the conversion of 1 μ mol of L-asparagine per reaction minute, per mg of protein.

Asparaginase erwinia chrysanthemi (recombinant)-rywn is produced by fermentation of a genetically engineered *Pseudomonas fluorescens* bacterium containing the DNA which encodes for asparaginase *Erwinia chrysanthemi*.

RYLAZE (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection is supplied as a sterile, clear to opalescent, colorless to slightly yellow, preservative-free solution for intramuscular injection. Each 0.5 mL contains 10 mg asparaginase erwinia chrysanthemi (recombinant)-rywn and the inactive ingredients: polysorbate 80 (0.1 mg), sodium chloride (1.5 mg), sodium phosphate dibasic anhydrous (0.8 mg), sodium phosphate monobasic monohydrate (0.6 mg), and trehalose dihydrate (32.1 mg). Sodium hydroxide may be added during manufacture to adjust the pH. The pH is approximately 7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Asparaginase erwinia chrysanthemi (recombinant)-rywn is an enzyme that catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia. The pharmacological effect 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.

12.2 Pharmacodynamics

Asparaginase erwinia chrysanthemi (recombinant)-rywn exposure-response relationships and the time course of pharmacodynamic response are unknown.

12.3 Pharmacokinetics

The pharmacokinetic parameters of asparaginase erwinia chrysanthemi (recombinant)-rywn are presented based on serum asparaginase activity (SAA) after administration of RYLAZE in pediatric and young adult patients with ALL or LBL, unless otherwise specified. Asparaginase erwinia chrysanthemi (recombinant)-rywn maximum SAA (C_{max}) and area under the SAA-time curve (AUC) increase proportionally over a dosage range from 12.5 to 50 mg/m² (0.25 to 1 times the maximum approved recommended dose of 50 mg/m²). The simulated exposures for asparaginase erwinia chrysanthemi (recombinant)-rywn after administration of the approved recommended dosages in a virtual population are summarized in Table 4.

Table 4: Simulated RYLAZE Pharmacokinetic Parameters Based on SAA

PK Parameter	Geometric Mean (%CV) After Last Dose		
	25 mg/m ² Intramuscularly Every 48 Hours	25/25/50 mg/m ² Intramuscularly Monday, Wednesday, Friday	
		Last 25 mg/m ² Wednesday morning dose	Last 50 mg/m ² Friday afternoon dose
C _{max} (U/mL)	2.3 (55%)	2.3 (54%)	4.1 (57%)
C _{trough} (U/mL)	0.46 (75%)	0.3 (75%) ^a	0.39 (87%) ^b

^a C_{trough} at maximum interval of 58 hours after the last 25 mg/m² Wednesday morning dose.

^b C_{trough} at maximum interval of 67 hours after the last 50 mg/m² Friday afternoon dose.

Absorption

The median (min, max) T_{max} of asparaginase erwinia chrysanthemi (recombinant)-rywn after intramuscular administration is 12 (8, 24) hours. The mean absolute bioavailability after intramuscular administration is 37% in healthy subjects.

Distribution

The geometric mean (%CV) volume of distribution of asparaginase erwinia chrysanthemi (recombinant)-rywn is 1.37 L/m² (47%).

Elimination

The geometric mean (%CV) clearance of asparaginase erwinia chrysanthemi (recombinant)-rywn is 0.17 L/hour/m² (42%) and the apparent half-life is 15.9 (11%) hours.

Metabolism

Asparaginase erwinia chrysanthemi (recombinant)-rywn is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

There were no clinically significant differences in the pharmacokinetics of asparaginase erwinia chrysanthemi (recombinant)-rywn based on age (1.4 to 25 years), weight (9 to 131 kg), or sex after the dose was adjusted by body surface area (BSA). The effect of renal and hepatic impairment on the pharmacokinetics of asparaginase erwinia chrysanthemi (recombinant)-rywn has not been studied.

Body Surface Area

The volume of distribution and clearance of asparaginase erwinia chrysanthemi (recombinant)-rywn increase with increasing BSA (0.44 to 2.53 m²).

Racial and Ethnic Groups

Black or African American patients had 29% lower clearance which may increase SAA exposure compared to White and Asian patients. There were no clinically significant differences in clearance between Hispanic and Non-Hispanic patients.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of RYLAZE or of other asparaginase erwinia chrysanthemi (recombinant) products.

During treatment in Study JZP458-201 (range 1 to 15 courses), 78/166 (47%) of patients treated with RYLAZE intramuscularly developed anti-asparaginase erwinia chrysanthemi (recombinant)-rywn antibodies. The effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, and effectiveness have not been adequately characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and impairment of fertility studies have not been conducted with asparaginase erwinia chrysanthemi (recombinant)-rywn.

In a fertility and early embryonic development study in rats, asparaginase *Erwinia chrysanthemi* had no effect on male or female fertility when administered intramuscularly at doses of up to 12 mg/m² (approximately 0.48 times the maximum recommended human dose) every other day for a total of 35 doses. In males, decreased sperm count was observed at all doses but did not impact fertility.

14 CLINICAL STUDIES

The efficacy of RYLAZE for the treatment of patients with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) who have developed hypersensitivity to *E. coli*-derived asparaginase as a component of a multi-agent chemotherapeutic regimen was evaluated in Study JZP458-201 (NCT04145531), an open-label, multi-cohort, multi-center trial. In this trial, RYLAZE was administered at various dosages and routes of administration every Monday, Wednesday, and Friday for a total of 6 doses to replace each dose of pegaspargase.

For the 225 evaluable patients, the median age was 10 years (range: 1-25 years); 61% were male and 39% were female; 69% were White, 11% were Black/African American, 4% were Asian, and 16% were of other or unknown race: 187 (83%) patients had experienced a hypersensitivity reaction (Grade \geq 3) to pegaspargase, and 15 patients (7%) reported silent 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 by simulation. Table 5 shows the proportion with NSAA \geq 0.1 U/mL for each approved dosage regimen based on simulation in a virtual population [see *Clinical Pharmacology* (12.3)].

Table 5: Proportion (95% CI) with NSAA \geq 0.1 U/mL by Simulation

RYLAZE Dosage	Trough Sampling Time	Proportion with NSAA \geq 0.1 U/mL (95%
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		CI) ^a
25 mg/m ² intramuscularly every 48 hours	48 hours	96.0 (94.4, 97.2)
25/25/50 mg/m ² intramuscularly Monday morning/Wednesday morning/Friday afternoon	Friday afternoon: 58 hours after 25 mg/m ² Wednesday morning dose ^b	91.6 (90.4, 92.8)
	Monday morning: 67 hours after 50 mg/m ² Friday afternoon dose ^c	91.4 (90.1, 92.6)

^a Based on 2,000 virtual subjects.

^b Based on maximum interval of 58 hours between the Wednesday morning and Friday afternoon doses.

^c Based on maximum interval of 67 hours between the Friday afternoon and Monday morning doses.

16 HOW SUPPLIED/STORAGE AND HANDLING

RYLAZE (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection is supplied as a sterile, clear to opalescent, colorless to slightly yellow, preservative-free solution in single-dose vials. Each single-dose vial (NDC 68727-900-01) contains 10 mg/0.5 mL asparaginase erwinia chrysanthemi (recombinant)-rywn. Each carton of RYLAZE (NDC 68727-900-03) contains 3 single-dose vials.

Store RYLAZE vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake or freeze.

17 PATIENT COUNSELING INFORMATION

- Hypersensitivity
Inform patients of the risk of allergic reactions, including anaphylaxis. Instruct the patient on the symptoms of allergic reactions and to seek medical advice immediately if they experience such symptoms [see *Warnings and Precautions (5.1)*].
- Pancreatitis
Instruct patients on signs and symptoms of pancreatitis and to seek medical attention if they experience severe abdominal pain [see *Warnings and Precautions (5.2)*].
- Thrombosis
Instruct patients on the risk of thrombosis and to seek medical advice immediately if they experience headache, arm or leg swelling, shortness of breath, and chest pain [see *Warnings and Precautions (5.3)*].
- Hemorrhage
Advise patients to report any unusual bleeding or bruising to their healthcare provider [see *Warnings and Precautions (5.4)*].

- Hepatotoxicity
Advise patients to report any jaundice, severe nausea or vomiting, or easy bleeding or bruising to their healthcare provider [*see Warnings and Precautions (5.5)*].
- Pregnancy
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with RYLAZE and for 3 months after the last dose [*see Use in Specific Populations (8.3)*].

- Lactation
Advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose [*see Use in Specific Populations (8.2)*].

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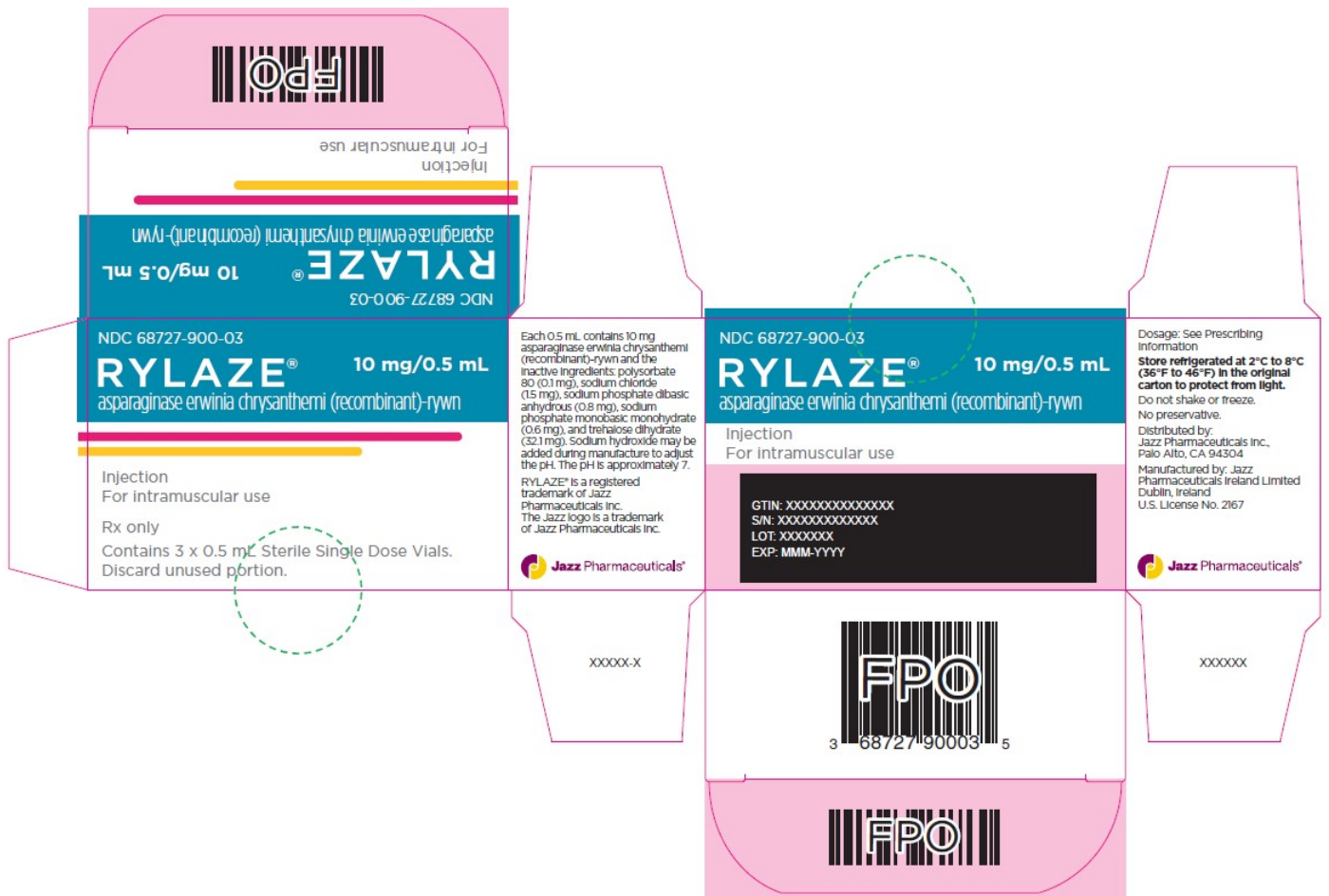
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PACKAGE/LABEL PRINCIPAL DISPLAY PANEL



Package/Label Display Panel

	<p>NDC 68727-900-01</p> <p>RYLAZE[®] asparaginase erwinia chrysanthemii (recombinant)-rywn 10 mg/0.5 mL</p> <p>INJECTION FOR INTRAMUSCULAR USE Rx Only</p> <p> Jazz Pharmaceuticals[®]</p> <p>XXXXX</p>	<p>Dosage: See Prescribing Information</p> <p>Store refrigerated at 2°C to 8°C (36°F to 46°F).</p> <p>Jazz Pharmaceuticals Ireland Limited</p> <p>U.S. License No. 2167</p> <p>XXXXXX</p>	<p>LOT XXXXXX</p> <p>EXP MMM-YYYY</p>
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3 vials (NDC 68727-900-01)
 1 carton (NDC 68727-900-03)
 asparaginase erwinia chrysanthemi (recombinant)-rywn
 RYLAZE™
 Injection, for intramuscular use
 10 mg/0.5 mL

RYLAZE				
asparaginase erwinia chrysanthemi (recombinant)-rywn injection				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68727-900	
Route of Administration	INTRAMUSCULAR			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
ASPARAGINASE (UNII: G4FQ3CKY5R) (ASPARAGINASE - UNII:G4FQ3CKY5R)		ASPARAGINASE	20 mg in 1 mL	
Inactive Ingredients				
Ingredient Name			Strength	
TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)			170 mmol in 1 mL	
SODIUM CHLORIDE (UNII: 451W47IQ8X)			50 mmol in 1 mL	
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)			11.6 mmol in 1 mL	
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)			8.5 mmol in 1 mL	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)			0.2 mg in 1 mL	
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68727-900-03	3 in 1 CARTON	06/30/2021	
1	NDC:68727-900-01	0.5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
BLA	BLA761179	06/30/2021		

Labeler - Jazz Pharmaceuticals, Inc. (135926363)

Registrant - Jazz Pharmaceuticals Ireland Limited (896650210)

