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

----------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----------
When replacing a long-acting asparaginase product, the recommended dosage of RYLAZE is 25 mg/m^2 administered intramuscularly every 48 hours. (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, fatigue, infection, headache, pyrexia, drug hypersensitivity, febrile neutropenia, decreased appetite, stomatitis, bleeding, and hyperglycemia. (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: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

When replacing a long-acting asparaginase product, the recommended dosage of RYLAZE is 25 mg/m^2 administered intramuscularly every 48 hours.

See the full prescribing information for the long-acting asparaginase product to determine the duration of administration of RYLAZE as replacement therapy.

2.2 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 1.

Table 1: Dosage Modifications

Adverse Reaction	Severity*	Action
Hypersensitivity Reaction *[see Warnings and Precautions (5.1)]*	Grade 2	• Treat the symptoms.
	Grade 3 to 4	• Discontinue RYLAZE permanently.
Pancreatitis *[see Warnings and Precautions (5.2)]*	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 Warnings and Precautions (5.3)]*	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 Warnings and Precautions (5.4)]*	Grade 3 to 4	• 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	• 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.

2.3 Preparation and Administration Instructions

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

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.

- Determine the dose, total volume of RYLAZE solution required, and the number of RYLAZE vials needed. More than one vial may be needed for a full dose.
- Withdraw the indicated injection volume of RYLAZE into the syringe for injection.
  - Do not shake the vial.
  - Limit the volume of RYLAZE at a single injection site to 2 mL.
  - If the volume to be administered is greater than 2 mL, divide the doses equally into multiple syringes, one for each injection site.
  - Discard the remaining unused RYLAZE in the single-dose vial.
- Administer RYLAZE by intramuscular injection within 4 hours after drawing the dose into the syringe(s).
  - 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 (15°C to 25°C [59°F to 77°F]) or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 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 25% of patients in clinical trials, and it was severe in 2% of patients *[see Adverse Reactions (6.1)]*. The median time from the first dose of RYLAZE to the onset of the first hypersensitivity event was 27 days (range 1-171 days). The most commonly observed reaction was rash (17%), and no patient experienced a severe rash. The median time from the first dose to the first onset of rash was 33.5 days (range 1-127 days).

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 (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.

5.2 Pancreatitis

Pancreatitis was reported in 14% of patients in clinical trials of RYLAZE and was severe in 6% *[see Adverse Reactions (6.1)]*. Clinical pancreatitis occurred in 5% of patients, and it was severe in 4% of patients. Elevated amylase or lipase without clinical diagnosis of pancreatitis was observed in 9% of patients, and it was severe in 2% 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 (2.2)].* 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 following treatment with L-asparaginase class products. 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 (2.2)]*.

5.4 Hemorrhage

Bleeding was reported in 17% of patients treated with RYLAZE, and it was severe in 1%. Most commonly observed reactions were bruising (8%) (contusion, increased tendency to bruise and injection site bruising) and nose bleeding (6%), which was severe in 1% of patients. Other observed bleeding reactions included hematuria (2%), disseminated intravascular coagulopathy (1%), rectal bleeding (1%) and gingival bleeding (1%) *[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 (2.2)]*.

5.5 Hepatotoxicity

Elevated bilirubin and/or transaminases occurred in 62% of patients treated with RYLAZE in clinical trials, and 12% 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 (2.2)]*.

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 to RYLAZE at various dosages, including dosages other than the recommended, used in combination with chemotherapy in 102 patients in JZP458-201 *[see Clinical Studies (14)]*. These patients received a median of 3 courses of RYLAZE (range: 1-14 courses); 38% of patients received at least four courses.

The safety of RYLAZE described below was evaluated in a cohort of 33 patients from JZP458-201 who received RYLAZE 25 mg/m^2 intramuscularly on Monday, Wednesday, and 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 to 24 years); the majority of patients were male (51%) and white (73%). The patients received a median of 4 courses of RYLAZE (range: 1-14 cycles); 48% of patients received at least four courses.

A fatal adverse reaction (infection) occurred in 1 patient treated with the RYLAZE 25 mg/m^2 dosage. Serious adverse reactions occurred in 55% of patients who received the RYLAZE 25 mg/m^2 dosage. The most frequent serious adverse reactions (in ≥ 5% of patients) were febrile neutropenia, dehydration, pyrexia, stomatitis, diarrhea, drug hypersensitivity, infection, nausea, and viral infection. Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received the RYLAZE 25 mg/m^2 dosage. Adverse reactions resulting in permanent discontinuation included hypersensitivity (6%) and infection (3%).

All patients treated with the RYLAZE 25 mg/m^2 dosage as a component of multi-agent chemotherapy developed neutropenia, anemia, or thrombocytopenia. The most common nonhematological adverse reactions in patients were abnormal liver test, nausea, musculoskeletal pain, fatigue, infection, headache, pyrexia, drug hypersensitivity, febrile neutropenia, decreased appetite, stomatitis, bleeding, and hyperglycemia. Table 2 shows the common adverse reactions occurring in at least 15% of the patients.

Table 2: Adverse Reactions (≥ 15% incidence) in Patients Receiving RYLAZE 25 mg/m^2 as a Component of Multi-Agent Chemotherapy in Study JZP458-201

Adverse Reaction	RYLAZE 25 mg/m^2 Dosage [a] N=33	
	All Grades (%)	Grades 3-4 (%)
Abnormal liver test*	70	12
Nausea*	46	9
Musculoskeletal pain*	39	6
Fatigue*	36	3
Infection*[b]	30	12
Headache	30	0
Pyrexia	27	6
Drug hypersensitivity*	24	6
Febrile neutropenia	24	24
Decreased appetite	21	6
Stomatitis	21	9
Bleeding*	21	0
Hyperglycemia	21	3
Abdominal pain*	18	0
Tachycardia*	18	0
Diarrhea*	18	6
Constipation	15	0
Dehydration	15	9
Neuropathy peripheral*	15	0
Cough	15	0
Insomnia	15	0

*Includes grouped terms
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.
[b] Does not include the following fatal adverse reactions: infection (N=1).
Safety data for patients treated on a Monday, Wednesday, and Friday schedule.

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

Gastrointestinal disorders: Abdominal discomfort, abdominal distension, pancreatitis
General disorders and administration site conditions: Infusion site reaction, pain
Infections and infestations: Viral infection, bacterial infection, fungal infection
Investigations: Blood fibrinogen decreased, activated partial thromboplastin time prolonged
Metabolism and nutrition disorders: Acidosis
Musculoskeletal and connective tissue disorders: Bone pain, muscular weakness, muscle spasms
Nervous system disorders: Paresthesia
Psychiatric disorders: Agitation, anxiety, irritability
Renal and urinary disorders: Acute kidney injury
Skin and subcutaneous disorders: Pruritus
Vascular disorders: Hypotension

6.2 Immunogenicity

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

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/m^2) and rabbits (at 0.12, 0.30, or 0.48 mg/m^2). In rats given 12 mg/m^2 (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/m^2 (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/m^2 (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 84 pediatric patients, including 2 infants (1 month to < 2 years), 62 children (2 years to < 12 years old), and 20 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 1µmol 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 (32.1 mg). Sodium hydroxide may be added 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) following administration of the approved recommended dosage in pediatric and young adult patients (1 to 24 years), unless otherwise specified. The exposures for asparaginase erwinia chrysanthemi (recombinant)-rywn are summarized in Table 3. 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/m^2 (0.5 to 2 times the approved recommended dose of 25 mg/m^2).

Table 3: RYLAZE Pharmacokinetic Parameters Based on SAA

Parameter	Dose in Course	Geometric Mean (%CV)
C_{max} (U/mL)	1	1.80 (40%)
	7	2.24 (42%)
C_{48h}[a] (U/mL)	1	0.33 (88%)
	7	0.40 (93%)
$AUC_{0\text{-}48h}$ (h·U/mL)	1	37.9 (39%)
	7	48.5 (41%)

[a] SAA 48 hours after the most recent dose

Absorption

The median t_{max} of asparaginase erwinia chrysanthemi (recombinant)-rywn is 10 hours. The mean absolute bioavailability for IM administration is 37% in healthy subjects.

Distribution

The geometric mean (%CV) apparent volume of distribution of asparaginase erwinia chrysanthemi (recombinant)-rywn is 1.48 L/m^2 (49%).

Elimination

The geometric mean (%CV) apparent clearance of asparaginase erwinia chrysanthemi (recombinant)-rywn is 0.31 L/hour/m^2 (36%) and the apparent half-life is 18.2 hours (16%).

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 to 52 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 apparent volume of distribution and apparent clearance of asparaginase erwinia chrysanthemi (recombinant)-rywn increase with increasing BSA (0.44 to 2.53 m^2).

Race and Ethnicity

Black (n=10) and Asian (n=5) patients had 29% lower clearance which may increase SAA exposure compared to White (n=61) patients. There were no clinically significant differences in clearance between Hispanic (n=28) and Non-Hispanic (n=53) patients.

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/m^2 (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, multicenter trial. A treatment course consisted of RYLAZE at various dosages administered intramuscularly every Monday, Wednesday, and Friday for a total of 6 doses to replace each dose of pegaspargase.

For the 102 patients treated, the median age was 10 years (range, 1 - 24 years); 57% were male and 43% were female; 73% were white, 12% were Black/African American, 5% were Asian, and 10% were of other or unknown race. Ninety-seven (94%) patients had experienced a hypersensitivity reaction to pegaspargase, and 6 patients (7%) had 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. The results of modeling and simulations showed that for a dosage of 25 mg/m^2 administered intramuscularly every 48 hours, the proportion of patients maintaining NSAA ≥ 0.1 U/mL at 48 hours after a dose of RYLAZE was 93.6% (95% CI: 92.6%, 94.6%) *[see Clinical Pharmacology (12.3)].*

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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