DOSING AND ORDERING GUIDE

RYLAZE™
asparaginase erwinia chrysanthemi (recombinant)-rywn for injection 10mg/0.5mL per vial

RELY ON RYLAZE–THE ONLY RECOMBINANT *ERWINIA* ASPARAGINASE FOR THE TREATMENT OF ALL/LBL[1]

ALL=acute lymphoblastic leukemia; LBL=lymphoblastic lymphoma.

Indication

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen given by intramuscular injection 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.

IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis
- Serious pancreatitis during previous asparaginase therapy

Please see additional Important Safety Information on pages 12-13 and full Prescribing Information.

DOSING

When replacing a long-acting asparaginase product, the recommended dosage of RYLAZE is:

- 25 mg/m^2 administered intramuscularly (IM) every 48 hours[1]

See the full Prescribing Information for the long-acting asparaginase product to determine the duration of administration of RYLAZE as replacement therapy.[1]

ADMINISTRATION

RYLAZE is administered by intramuscular injection.[1]

- Limit the volume of RYLAZE at a single injection site to 2 mL[1]
- If the volume to be administered is greater than 2 mL, divide the dose equally into multiple syringes, 1 for each injection site[1]
- Administer RYLAZE by intramuscular injection within 4 hours after drawing the dose into the syringe(s)[1]
  - 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 59°F to 77°F or refrigerated at 36°F to 46°F for up to 4 hours. The syringe does not need to be protected from light during storage
- Ensure that medical support is available to appropriately manage anaphylactic reactions when administering RYLAZE[1]

PREPARATION

- Ready-to-use formulation[1,2]
  - No reconstitution required
  - No filtration required
- Visually inspect RYLAZE for particulate matter, cloudiness, or discoloration prior to administration. If any of these are present, discard the vial[1]
- Discard partially used or empty vials of RYLAZE[1]
- Do not shake[1]

STORAGE AND HANDLING

RYLAZE for injection is supplied as a sterile, clear to opalescent, colorless to slightly yellow, preservative-free solution in single-dose vials. Each single-dose vial contains 10 mg/0.5 mL.[1]

- RYLAZE does not contain a preservative[1]
- Each carton of RYLAZE contains 3 single-dose vials[1]
- Store RYLAZE refrigerated at 36°F to 46°F in the original carton to protect from light[1]
- Do not freeze[1]

IMPORTANT SAFETY INFORMATION

Contraindications (continued)

RYLAZE is contraindicated in patients with a history of:

- Serious thrombosis during previous asparaginase therapy
- Serious hemorrhagic events during previous asparaginase therapy

Please see additional Important Safety Information on pages 12–13 and full Prescribing Information.

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RECOMMENDED MONITORING AND DOSAGE MODIFICATIONS

Monitor patient's bilirubin, transaminase, and glucose levels, and clinical examinations prior to treatment every 2-3 weeks and as indicated clinically.[1]

- If results are abnormal, monitor patients until recovery from the cycle of therapy[1]
- If an adverse reaction occurs, modify treatment according to the table below[1]

Adverse Reaction	Severity*	Action
Hypersensitivity Reaction	Grade 2	• Treat the symptoms
	Grade 3 to 4	• Discontinue RYLAZE permanently
Pancreatitis	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	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	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	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.

ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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. The median time from the first dose of RYLAZE to the onset of the first hypersensitivity event was 27 days (range 1-171 days).

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HOW TO CALCULATE DOSE VOLUME

To calculate for dose volume:

- Each **single-dose vial** of RYLAZE contains 10 mg/0.5 mL[1]
- Use the chart to determine the injection volume based on patient's body surface area (BSA)[1]
  - Calculate the total volume of RYLAZE solution required for each dose:

$$\text{Volume (mL)} = \text{BSA } (m^2) \times \text{Dose } (25 \text{ mg}/m^2) \div \text{Concentration } (20 \text{ mg/mL})$$

- Injection volume should be rounded based on institutional standard of care
- It is solely the responsibility of the treating healthcare professional and/or institution to determine the appropriate dosage for each patient and to appropriately account for any unused drug or wastage in accordance with any applicable law, regulation, or policy
- Healthcare professionals should calculate all doses before administration. This vial usage chart is merely a guide and is not a substitute for, nor intended to influence, the independent judgment of healthcare professionals. Neither Jazz Pharmaceuticals nor its contractors accept any responsibility for the applicability of the information provided to any particular clinical situation or for any actions or decisions taken in calculating or administering the dose

VIAL DOSAGE SCHEDULE

BSA (m^2)	Injection volume based on BSA, mL	Number of vials per 25 mg/m^2 dose
0.4	0.5	1
0.5	0.63	2
0.6	0.75	2
0.7	0.88	2
0.8	1	2
0.9	1.13	3
1.0	1.25	3
1.1	1.38	3
1.2	1.5	3
1.3	1.63	4
1.4	1.75	4
1.5	1.88	4
1.6	2	4
1.7	2.13	5
1.8	2.25	5
1.9	2.38	5
2.0	2.5	5
2.1	2.63	6
2.2	2.75	6
2.3	2.88	6
2.4	3	6

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (continued)

Hypersensitivity Reactions

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).

Please see additional Important Safety Information on pages 12-13 and full Prescribing Information.

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RYLAZE ORDERING INFORMATION

Specialty Distribution Partners

RYLAZE is available for purchase from the authorized Specialty Distributors listed below. Verify that your facility has an account with their Specialty Distributor before ordering. If not, they should contact their Specialty Distributor. The facility should also contact their Specialty Distributor with questions regarding product returns.

AmerisourceBergen

ASD Healthcare

RYLAZE Item #: 10259717
Online: https://www.asdhealthcare.com
Phone: 1-800-746-6273
Fax: 1-800-547-9413
Email: asd.customerservice@asdhealthcare.com
- Orders can be placed Monday-Thursday, 7:00 AM-6:30 PM CT; Friday, 7 AM-6 PM CT
- For emergency orders after hours of service, call 1-800-746-6273

Oncology Supply

RYLAZE Item #: 10259764
Online: https://www.oncologysupply.com
Phone: 1-800-633-7555
Fax: 1-800-248-8205
Email: custserv@oncologysupply.com
- Orders can be placed Monday-Friday, 9 AM-8 PM CT
- Orders placed after hours via Oncology Supply's email address are processed the next business day

Cardinal Health

Cardinal Specialty Pharmaceutical Distribution

RYLAZE Item #: 5731948
Online: Order Express
https://orderexpress.cardinalhealth.com
Specialty Online
https://specialtyonline.cardinalhealth.com
Phone: 1-877-453-3972
Fax: 1-877-274-9897
Email: SPDOncologyTeam@cardinalhealth.com
- Orders can be placed Monday-Friday, 8 AM-7 PM CT
- For emergency orders after hours of service, call 1-877-453-3972

McKesson Specialty Health

McKesson Plasma and Biologics

RYLAZE Item #: 2338747
Online: https://connect.mckesson.com
Phone: 1-877-625-2566
Fax: 1-888-752-7626
Email: MPBOrders@mckesson.com
- Orders can be placed Monday-Friday, 9:00 AM-7:30 PM ET
- Email for all other information requests: MPB@mckesson.com
- For emergency orders after hours of service, call 1-877-625-2566

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (continued)

Hypersensitivity Reactions

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.

Please see additional Important Safety Information on pages 12-13 and full Prescribing Information.

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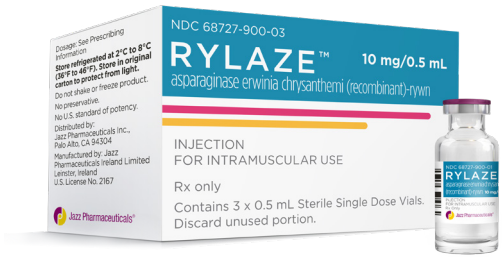
RYLAZE CODING INFORMATION

Miscellaneous J-codes		
J3490	J3590	J9999

Product J-code to come in 2022.

NDC		
10-digit	**11-digit**	Carton containing 3 vials of RYLAZE
68727-900-03	68727-0900-03	

Payers may require a 10-digit or 11-digit NDC. Both are provided for your convenience. These are sample codes based on publicly available information and are informational only and not a guarantee or promise of coverage. Appropriate codes can vary by patient, setting of care, and payer. Correct coding is the responsibility of the provider submitting the claim for the item or service. Please check with the payer to verify codes and special billing requirements.



NDC=National Drug Code.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (continued)

Hypersensitivity Reactions

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). Discontinue RYLAZE in patients with serious hypersensitivity reactions.

Please see additional Important Safety Information on pages 12–13 and full Prescribing Information.

PATIENT SUPPORT SERVICES

JazzCares® supports healthcare providers and office staff with coverage and reimbursement support[a] so appropriate patients can get access to RYLAZE and reduce their out-of-pocket costs.[b]

JazzCares

Assists you with benefits investigations, prior authorizations and appeals,[a] and referrals to other financial assistance options for eligible patients

Savings Card

Eligible, commercially insured patients can pay as little as $10 for their RYLAZE medication, subject to an annual maximum (restrictions apply)[a]

Free Drug Program

Uninsured or underinsured patients who meet certain financial criteria may be eligible to receive RYLAZE at no cost[b]

Learn more about JazzCares support offerings by calling 1-833-533-JAZZ (5299) Monday–Friday, 8 AM–8 PM ET, or visiting jazzcares.com/hcp/rylaze.

[a]Insurance coverage and plans may vary. JazzCares provides general information only and is not a guarantee of any coverage or reimbursement outcome. All treatment decisions rest solely with the treating physician or qualified healthcare professional.
[b]Subject to eligibility requirements and terms and conditions.

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IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis
- Serious pancreatitis during previous asparaginase therapy
- Serious thrombosis during previous asparaginase therapy
- Serious hemorrhagic events during previous asparaginase therapy

Warnings and Precautions

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. 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). Discontinue RYLAZE in patients with serious hypersensitivity reactions.

Pancreatitis

Pancreatitis was reported in 14% of patients in clinical trials of RYLAZE and was severe in 6%. 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. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.

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.

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%).

In patients treated with 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.

Hepatotoxicity

Elevated bilirubin and/or transaminases occurred in 62% of patients treated with RYLAZE in clinical trials, and 12% had Grade ≥3 elevations.

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.

Adverse Reactions

Serious adverse reactions occurred in 55% of patients who received RYLAZE. The most frequent serious adverse reactions (in ≥5% of patients) were febrile neutropenia, dehydration, pyrexia, stomatitis, diarrhea, drug hypersensitivity, infection, nausea, and viral infection.

The most common adverse reactions (incidence >20%) with RYLAZE are abnormal liver test (70%), nausea (46%), musculoskeletal pain (39%), fatigue (36%), infection (30%), headache (30%), pyrexia (27%), drug hypersensitivity (24%), febrile neutropenia (24%), decreased appetite (21%), stomatitis (21%), bleeding (21%), and hyperglycemia (21%).

Use in Specific Populations

Pregnancy and Lactation

RYLAZE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with RYLAZE and for 3 months after the last dose. Advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose.

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For more information about RYLAZE, visit RYLAZE.com.

Please see Important Safety Information throughout and full Prescribing Information.

References: 1. RYLAZE [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Maese L, Rizzari C, Coleman R, et al. Can recombinant technology address asparaginase *Erwinia chrysanthemi* shortages? *Pediatr Blood Cancer*. 2021;e29169. doi:10.1002/pbc.29169.

Jazz Pharmaceuticals