BLA 761179/S-007

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals Ireland Limited
c/o Jazz Pharmaceuticals, Inc.
Attention: Matthew T. Vitagliano
Associate Director, Global Regulatory Affairs
2005 Market Street, Suite 2100
Philadelphia, PA 19103

Dear Matthew T. Vitagliano:

Please refer to your supplemental biologics license application (sBLA), dated March 8, 2024, received March 8, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection, for intramuscular use.

We also refer to our letter dated January 12, 2024, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for the asparaginase class. This information pertains to the risk of hepatic veno-occlusive disease.

This supplemental biologics license application provides for revisions to the labeling for Rylaze (asparaginase erwinia chrysanthemi (recombinant)). The agreed upon changes to the language included in our January 12, 2024, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough)~~.

1. Highlights of Prescribing Information:

   Contraindications:
   RYLAZE is contraindicated in patients with (b) (4)

   History of serious hypersensitivity reactions to RYLAZE, including anaphylaxis. (4)
   History of serious pancreatitis during previous L-asparaginase therapy. (4)
   History of serious thrombosis during previous L-asparaginase therapy. (4)
   History of serious hemorrhagic events during previous L-asparaginase therapy. (4)
   Severe (b) (4) hepatic impairment. (4)

   Warnings and Precautions:
   Hepatotoxicity, including hepatic veno-occlusive disease (b) (4)

2. Section 4, Contraindications:

   RYLAZE is contraindicated in patients with (b) (4)

   History of serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis *[see Warnings and Precautions (5.1)]*;
   History of serious pancreatitis during previous asparaginase therapy *[see Warnings and Precautions (5.2)]*;
   History of serious thrombosis during previous asparaginase therapy *[see Warnings and Precautions (5.3)]*;
   History of serious hemorrhagic events during previous asparaginase therapy *[see Warnings and Precautions (5.4)]*.
   Severe hepatic impairment *[see Warnings and Precautions (5.5)].*

3. Section 5.5, Hepatotoxicity, including Hepatic Veno-Occlusive Disease

   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)].

   Hepatotoxicity, including severe, life-threatening, and potential (b) (4) fatal cases of hepatic veno-occlusive disease (VOD), have been observed in patients treated with asparaginase class products in combination with standard chemotherapy, including during the induction phase of multiphase chemotherapy [see ADVERSE REACTIONS (6)]. Do not administer RYLAZE to patients with severe hepatic impairment [see Contraindications (4)]. Inform patients of the signs and symptoms of hepatotoxicity.

   Evaluate bilirubin and transaminases prior to each cycle of RYLAZE and at least weekly during cycles of treatment that include RYLAZE, through (b) (4) four weeks after the last dose of RYLAZE. Monitor frequently for signs and symptoms of hepatic VOD, which may include rapid weight gain, fluid retention with ascites, hepatomegaly (which may be painful), and rapid increase of bilirubin. For patients who develop abnormal liver tests after RYLAZE, more frequent monitoring for liver test abnormalities and clinical signs and symptoms of VOD is recommended. In the event of serious liver toxicity, including VOD, discontinue treatment with RYLAZE and provide supportive care [see Dosage and Administration (2.3)].

4. Section 6, Adverse Reactions:

   Hepatotoxicity, including VOD [see WARNINGS AND PRECAUTIONS (5.7)]

5. Section 6.2, Postmarketing Experience:

   The following adverse reactions have been identified during post approval use of RYLAZE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

   Hepatic: Veno-occlusive disease (VOD)

6. Section 17, Patient Counseling Information:

   Hepatotoxicity, including Veno-Occlusive Liver Disease (b) (4)

   Inform patients that liver problems, including severe, life-threatening, or fatal VOD and abnormalities in liver tests, may develop during RYLAZE treatment. Advise patients to (b) (4) report any jaundice, severe nausea or vomiting, or easy bleeding or bruising to their healthcare provider (b) (4) [see WARNINGS AND PRECAUTIONS (5.6)]."

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling, with minor editorial revisions listed below and reflected in the enclosed labeling.

- Included Section 4, Contraindications in the Recent Major Changes in Highlights.
- Updated the Revised date in Highlights.
- Added a bullet for the last contraindication in Section 4.
- Added a vertical line in the left margin in the full prescribing information for the last contraindication in Section 4.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Stacie Woods, Safety Regulatory Project Manager, at 301-796-4803, or via email at Stacie.Woods@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Shan M. Pradhan, M.D.
Associate Director for Safety
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHAN PRADHAN
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