BLA 761179

BLA APPROVAL

Jazz Pharmaceuticals Ireland Limited
c/o Jazz Pharmaceuticals, Inc.
Attention: Wheatley Spence, MS
Senior Director, Regulatory Affairs
2005 Market Street, Suite 2100
Philadelphia, PA 19103

Dear Ms. Spence:

Please refer to your biologics license application (BLA) dated April 30, 2021, received April 30, 2021, 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.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2167 to Jazz Pharmaceuticals Ireland Limited, Leinster, Ireland, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product RYLAZE (asparaginase erwinia chrysanthemi (recombinant)-rywn). 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.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture asparaginase erwinia chrysanthemi (recombinant)-rywn drug substance at (b) (4) (b) (4) The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4) (b) (4) You may label your product with the proprietary name, RYLAZE, and market it in 10 mg solution in a 0.5 mL single-dose vial for intramuscular injection.

DATING PERIOD

The dating period for RYLAZE shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at ≤ (b) (4) °C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of RYLAZE to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of RYLAZE, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

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.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). 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 (October 2009)*.[2]

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

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on June 17, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761179**." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that your request for a rare pediatric disease priority review voucher is denied. This application is not eligible for a rare pediatric priority review voucher because it was not deemed eligible for priority review. See section 529(a)(4)(C) of the FD&C Act.

ADVISORY COMMITTEE

Your application for asparaginase erwinia chrysanthemi (recombinant)-rywn) was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study for ages < 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4112-1 Conduct a clinical trial to determine the appropriate dose of JZP-458 by the intravenous route and to assess safety, pharmacokinetics, and pharmacodynamics of JZP-458 administered by the intravenous route in pediatric patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Include at least 6 patients < 6 years old, 6 patients 6-11 years old and 6 patients 12-17 years old.

Final Protocol Submission:	07/2021
Study Completion:	06/2022
Final Report Submission:	12/2022

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 129622 with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4112-2 Conduct an assessment of the binding and neutralizing anti-drug antibody (ADA) responses in all JZP-458 treated patients from Study JZP458-201 with a validated assay (requested in PMC 4112-3 and PMC 4112-4) capable of sensitively detecting ADA responses in the presence of JZP-458 levels that are expected to be present in the serum at the time of patient sampling. Include information on the level of JZP-458 in each patient's test sample at each sampling point and an assessment of the effects of binding and neutralizing ADA on clinical hypersensitivity reactions in the final report. In addition, assess the effects of binding and neutralizing ADA on JZP-458 exposure (serum asparaginase activity and serum asparaginase content) in the final report.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on June 28, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2022
Final Protocol Submission:	05/2022
Study Completion:	08/2022
Final Report Submission:	12/2022

4112-3 Develop and validate a binding anti-drug antibody (ADA) assay with sufficient drug tolerance to be able to detect, confirm, and titer anti-Rylaze binding antibodies in the presence of Rylaze concentrations in clinical samples at the time of sampling.

The timetable you submitted on June 28, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2021
Final Protocol Submission:	10/2021
Study Completion:	12/2021
Final Report Submission:	02/2022

4112-4 Develop and validate a neutralizing ADA (NAb) assay with sufficient drug tolerance to detect neutralizing antibodies against Rylaze in the presence of expected Rylaze concentrations in clinical samples at the time of sampling.

The timetable you submitted on June 28, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2022
Final Protocol Submission:	05/2022
Study Completion:	07/2022
Final Report Submission:	09/2022

4112-5 Conduct a study examining quantitative recovery of anti-JZP458 antibodies from serum samples pretreated with Melon Gel Spin Plate Kit if immunogenicity data from an assay that uses the Melon Gel Spin Plate kit are used to support the license.

The timetable you submitted on June 28, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2021
Final Protocol Submission:	11/2021

Study Completion: 12/2021
Final Report Submission: 02/2022

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4112-6 To define and implement bioburden limits for routine reactivation of chromatography resins after extended storage.

The timetable you submitted on June 23, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021

4112-7 To repeat the bacterial retention study (b) (4) (b) (4) Once (b) (4) validated, monitoring (b) (4) will be implemented during routine manufacturing.

The timetable you submitted on June 23, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2022

4112-8 To update the container closure integrity test method to include a (b) (4)-µm breached positive control.

The timetable you submitted on June 23, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021

4112-9 To update the RP-UHPLC method validation to include impurities spiking study (e.g. pre-peaks and post-peaks are enriched to assess assay performance at different purity/impurity ratios).

The timetable you submitted on June 23, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2022

Submit clinical protocols to your IND 129622 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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*.[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Esther Park, Senior Regulatory Health Project Manager, at (301) 796-2811.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Acting Supervisory Associate Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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/

MARC R THEORET
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