

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761179Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 24, 2021
Requesting Office or Division: Division of Cardiology and Nephrology (DCN)
Application Type and Number: BLA 761179
Product Name and Strength: Rylaze (asparaginase Erwinia chrysanthemi (recombinant)-rywn)* injection, 20 mg/mL(10 mg/0.5 mL)
Applicant/Sponsor Name: Jazz Pharmaceuticals Ireland Limited
OSE RCM #: 2020-2594-1
DMEPA Safety Evaluator: Mariette Aidoo, PharmD, MPH
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 17, 2021 for Rylaze (asparaginase Erwinia chrysanthemi (recombinant)-rywn). We reviewed the revised container label and carton labeling for Rylaze (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Aidoo, M. Label and Labeling Review for Rylaze (BLA 761179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 6. RCM No.: 2020-2594.

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/s/

MARIETTE A AIDOO
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HINA S MEHTA
06/24/2021 10:27:35 AM

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 06/24/21

To: Esther Park, Regulatory Project Manager, DHM1

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Acting Deputy Director DAPR1, OPDP

Subject: OPDP Labeling Comments for RYLAZE™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection, for intramuscular use

BLA: 761179

In response to DHM1's consult request dated March 16, 2021, OPDP has reviewed the proposed product labeling for the original BLA submission for RYLAZE™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection, for intramuscular use (Rylaze).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling emailed to OPDP on June 23, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at rachael.conklin@fda.hhs.gov.

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	(b) (4)	OPDP notes that Table 2 of the PI includes a number of additional adverse reactions at rates >10%. For instance: Infection (30%) Febrile neutropenia (24%) Stomatitis (21%) Hemorrhage (21%) Hyperglycemia (21%) Constipation (18%) Dehydration (18%) Neuropathy peripheral (18%) Cough (18%) Insomnia (18%) OPDP recommends revising the presentation of the ARs in the Highlights to include all of the adverse reactions with an incidence >10%. Additionally, OPDP recommends revising the ARs presented in the Highlights section so that they appear in descending order (e.g., musculoskeletal pain (39%) should follow nausea).

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/s/

RACHAEL E CONKLIN
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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 3, 2021

TO: R. Angelo De Claro, M.D.
Director (Acting)
Division of Hematologic Malignancies I (DHM-I)
Office of Oncologic Diseases
Office of New Drugs Clinical

FROM: Amanda Lewin, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Kimberly Benson, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Julia Cho, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sean Kassim, Ph.D.
Director
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote Record Review (RRR) (b) (4)
(b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of serum asparaginase activity (SAA) assay, serum asparaginase content (SAC) assay, and anti-drug antibody (ADA)/neutralizing antibody (Nab) assays assessing the samples from studies JZP458-101 and JZP458-201 (BLA 761179; JZP-458, a recombinant form of asparaginase erwinia chrysanthemi, also termed RC-P) conducted at (b) (4)
(b) (4)

We observed objectionable conditions that impact the reliability of some study data.

1.1. Recommendation

(b) (4)

Based on our review of the RRR observations and the firm's response, we conclude the observations impact the reliability of some data from the audited studies. The firm will conduct additional validation experiments to address the observations. Following the receipt of updated method validation reports, the review division should consider the impact of the presence of the drug above the validated drug tolerance limit on the ADA assay and the impact of ADAs on the quantification of serum asparaginase.

2. Reviewed Studies

Study JZP458-101 (BLA 761179)

"A Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of RC-P in Healthy Adult Subjects"

Sample Analysis Period: 1/29/2019 - 4/25/2019 (SAA)
3/25/2019 - 4/30/2019 (SAC)

Study JZP458-201 (BLA 761179)

"An Open-Label, Multicenter Study of RC-P in Patients with Acute Lymphoblastic Leukemia (ALL)/Lymphoblastic Lymphoma (LBL) Following Hypersensitivity to E. coli-derived Asparaginases"

Sample Analysis Period: 4/17/2020 - 12/16/2020 (SAA)
5/25/2020 - 12/17/2020 (SAC)
9/10/2020 - 12/19/2020 (ADA/NAB)

Study JZP458-201 and the corresponding sample analyses are still ongoing. The dates above are for the first data cutoff for sample analysis.

3. Scope of RRR

OSIS scientists Amanda Lewin, Ph.D., Kimberly Benson, Ph.D., and Julia Cho, Ph.D. reviewed the analytical portions of the above studies conducted at (b) (4) from (b) (4).

The RRR included a thorough examination of method validation and sample analysis activities for the studies listed above, as well as evaluation of the instruments and the facility and interviews with the firm's management and staff. For study JZP458-201, we reviewed study sample analysis prior to data cutoff 1 (December 2020) and included in reports 00350550 (SAA), 00350551 (SAC), and 00350552 (ADA/NAB).

4. RRR Observations

(b) (4)

At the conclusion of the RRR, we observed objectionable conditions that impact reliability of study data. We discussed the following items with the firm's management during the RRR close-out meeting.

Our evaluation of the observations and the firm's written response dated (b) (4) (**Attachment 1**) are presented below.

4.1. Observations discussed at the close-out of RRR

(b) (4)

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4.2 Additional Information

The firm used human serum from healthy volunteers to establish the screening and confirmatory cut points for the ADA and NAb assays used in Study JZP458-201. During the RRR, the firm stated that they are currently in the process of evaluating whether the cut point established in the method validation is relevant for the in-patient study population. We recommend that the review division request the results of this evaluation.

5. Conclusion

Based on our review of the RRR observations and the firm's response, we conclude the RRR observations may impact the reliability of data from the audited studies. Following the availability of the updated method validation reports, the review division should consider the impact of drug concentrations above the validated drug tolerance in samples analyzed in the ADA assay and the impact of ADAs on the SAC assay.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Choi/Skelly/Au/Lewin

(b) (4)

Draft: AL 5/26/2021; JC 5/27/2021; KAB 6/3/2021

Edit: SK 6/3/2021

ECMS: <http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f883b8a4e3>

OSIS File #: (b) (4)

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/s/

AMANDA E LEWIN
06/03/2021 02:36:56 PM

KIMBERLY A BENSON
06/03/2021 02:39:25 PM

SEONGEUN CHO
06/03/2021 02:55:01 PM

SEAN Y KASSIM
06/03/2021 02:56:07 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 6, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	BLA 761179
Product Name, Dosage Form, and Strength:	Rylaze (asparaginase Erwinia chrysanthemi (Recombinant)-xxxx)* injection, 20 mg/mL (10 mg/0.5 mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
FDA Received Date:	December 9, 2020 and March 15, 2021
OSE RCM #:	2020-2594
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

* The non-proprietary name suffix for this BLA has not yet been determined; therefore, the placeholder, asparaginase Erwinia chrysanthemi (Recombinant)xxxx, is used throughout this review to refer to the nonproprietary name and suffix for this product.

1 REASON FOR REVIEW

As part of the approval process for 351(a) BLA 761179 Rylaze (asparaginase *Erwinia chrysanthemi* (Recombinant)-xxxx) injection, this review evaluates the proposed Rylaze prescribing information (PI), container label and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Jazz submitted BLA 761179 to obtain marketing approval for Rylaze (asparaginase *Erwinia chrysanthemi* (Recombinant)-xxxx) injection. Rylaze is an asparaginase specific enzyme proposed as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adults and pediatric patients who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase.

We evaluated the proposed prescribing information, container label and carton labeling to determine if it is acceptable from a medication error perspective. For the Division, we note the PI lacks clarity on frequency of administration which may confuse the user. We identified areas of the proposed label and labeling that could be revised to improve clarity and readability of important information. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Rylaze Prescribing Information, container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide specific recommendations in Section 4.1 for the Division and 4.2 for the Applicant below.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Highlights of Prescribing Information

1. We recommend replacing all instances of the proprietary name with the conditionally acceptable proprietary name 'Rylaze'.

2.

[REDACTED] (b) (4)

B. Prescribing Information

1. We recommend replacing all instances of the proprietary name with the conditionally acceptable proprietary name 'Rylaze'.

4.2 RECOMMENDATIONS FOR JAZZ PHARMACEUTICALS IRELAND LIMITED

We recommend the following be implemented prior to approval of this BLA:

A. Container Labels

1. We recommend removing the "per vial" statement next to the strength. This is not needed and to enhance readability of the strength.

B. Carton Labeling

1. For the side panel labeling, please revise [REDACTED] (b) (4)

[REDACTED] to prevent confusion.

2. We recommend revising the storage statement to "Store refrigerated at 2°C to 8°C (36°F to 46°F). Store in original carton to protect from light."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rylaze received on March 15, 2021 from Jazz Pharmaceuticals Ireland Limited.

Table 2. Relevant Product Information for Rylaze	
Initial Approval Date	N/A
Nonproprietary Name	asparaginase Erwinia chrysanthemi (Recombinant)-xxxx
Indication	Treatment of patients with acute lymphoblastic leukemia (ALL)/ lymphoblastic lymphoma (LBL) in adult and pediatric patients who have developed hypersensitivity or silent inactivation to <i>E. coli</i> -derived asparaginase. (NOTE: PI has not been submitted yet; information from Cover Letter)
Route of Administration	Intramuscular or Intravenous
Dosage Form	Injection
Strength	10 mg/0.5 mL
Dose and Frequency	Regimen 1: The recommended dose is 25 mg/m ² administered intramuscularly Monday and Wednesday and 50 mg/m ² on Friday for a total of six doses every two weeks to replace each planned dose of long-acting <i>E.coli</i> asparaginase. Regimen 2: The recommended dose is 25 mg/m ² administered intramuscularly every 48 hours for two weeks for a total 7 doses for each scheduled dose of long-acting <i>E.coli</i> asparaginase.
How Supplied	Single-dose vials
Storage	36°F to 46°F (2°C to 8°C)
Container Closure	2 mL glass vials

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 7, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'erwinaze' and 'asparaginase'. Our search identified two previous reviews^{a,b}, and we considered our previous recommendations to see if they are applicable for this current review.

^a Rutledge, M. Label and Labeling Review for Erwinaze (BLA 125359/085). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 27. RCM No.: 2014-593.

^b Toyer, D. Label and Labeling Review for Elspar (BLA 101063). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 AUG 3. RCM No.: 2009-839.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Rylaze labels and labeling submitted by Jazz Pharmaceuticals Ireland Limited.

- Container label received on March 15, 2021
- Carton labeling received on March 15, 2021
- Prescribing Information (Image not shown) received on March 15, 2021, available from [\\CDSESUB1\evsprod\bla761179\0017\m1\us\jzp-458_nda-label-252550mg_vx0_15mar21_clean.pdf](\\CDSESUB1\evsprod\bla761179\0017\m1\us\jzp-458_nda-label-252550mg_vx0_15mar21_clean.pdf)

G.2 Label and Labeling Images

Rylaze 10 mg/0.5 mL Vial Label

(b) (4)



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MARIETTE A AIDOO
05/06/2021 12:03:37 PM

HINA S MEHTA
05/06/2021 01:13:28 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/29/2021

TO: Division of Hematologic Malignancies I (DHMI)
Office of Oncologic Diseases (OOD)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761179

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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JAMES J LUMALCURI
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