CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761179
PDUFA Goal Date	April 30, 2022
OSE RCM #	2020-2593
Reviewer Name(s)	Somya Dunn, MD
Team Leader	Carolyn Tieu, Pharm.D., MPH
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 29, 2021
Subject	Evaluation of Need for a REMS
Established Name	Asparaginase erwinia chrysanthemi (recombinant)-rywn
Trade Name	Rylaze
Name of Applicant	Jazz Pharmaceuticals Ireland Limited
Therapeutic Class	Asparagine-specific enzyme
Formulation(s)	10 mg/0.5 mL solution in a single-dose vial
Dosing Regimen	25 mg/m^2 administered intramuscularly every 48 hours for a total of seven doses, or 25 mg/m^2 on Mondays and Wednesdays and 50 mg/m^2 on Fridays for a total of six doses.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rylaze (asparaginase erwinia chrysanthemi [recombinant]-rywn) injection is necessary to ensure the benefits outweigh its risks. Jazz Pharmaceuticals Ireland Limited submitted a Biologics License Application (BLA) 761179 for Rylaze with the proposed indication as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) in adults and pediatric patients one month or older who have developed hypersensitivity to *Escherichia coli*-derived asparaginase. The Applicant did not submit a REMS with this application.

DRM has determined a REMS is not necessary to ensure the benefits of Rylaze outweigh its risks. The expected benefit and risk profile of Rylaze are comparable to those of the currently approved asparaginase products. The most concerning adverse reactions observed with the use of Rylaze and the class of asparaginase products are hypersensitivity, pancreatitis, thrombosis, hemorrhage, and hepatotoxicity. These risks are communicated through labeling and there are no Boxed Warnings or REMS for these products. The likely prescribers are oncologists, and should be knowledgeable on treating this patient population and mangaging the risks associated with asparaginase products.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rylaze (asparaginase erwinia chrysanthemi [recombinant]-rywn) injection is necessary to ensure the benefits outweigh its risks. Jazz Pharmaceuticals Ireland Limited submitted a Biologics License Application (BLA) 761179 for Rylaze with the proposed indication as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) in adults and pediatric patients one month or older who have developed hypersensitivity to E. coli-derived asparaginase.[1] The Applicant did not submit a REMS with this application but proposed describing the risks of hypersensitivity, pancreatitis, thrombosis, hemorrhage, and hepatotoxicity in the *Prescribing Information* in the sections for *Contraindications, Warnings* and *Precautions* and *Patient Counseling Information.*

2 Background

2.1 PRODUCT INFORMATION

Rylaze is a NME BLA type 351(a) pathway application.[a] It is an asparaginase; an enzyme specific to asparagine with a proposed indication as a component of a multi-agent chemotherapeutic regimen for

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

the treatment of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) in adults and pediatric patients one month or older who have developed hypersensitivity to *E. coli*-derived asparaginase. Asparaginase *Erwinia chrysanthemi* catalyzes the conversion of the amino acid L-asparagine into aspartic acid. It also catalyzes the conversion of the amino acid L-glutamine into glutamic acid and ammonia. Leukemic cells cannot synthesize asparagine due their deficiency in asparagine synthetase activity. The mechanism of action as a chemotherapeutic agent is likely based leukemic cell dependence on exogenous asparagine for metabolism. The deficiency in asparagine leads to leukemic cell cytotoxicity. Rylaze is a recombinant crisantaspase produced in *Pseudomonas fluorescens*. It has the identical amino acid sequence to native *Erwinia* asparaginase, has been formulated to maintain stability and bioavailability after intramuscular (IM) injection and does not require reconstitution. It also exerts catalytic effect on glutamine which causes a depletion of asparagine, thus complementing the asparagine depletion from leukemic cells.

The proposed recommended dose of Rylaze is 25 mg/m^2 administered IM every 48 hours for a total of seven doses or 25 mg/m^2 on Mondays/Wednesdays and 50 mg/m^2 on Fridays for a total of six doses. [b] It is not approved in any other country at this time.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for Rylaze (BLA 761179) relevant to this review:

- 09/23/2020: Rylaze granted the designation of a rare pediatric disease product for the treatment of ALL.
- 12/09/2020: Applicant requested a rare pediatric disease priority review voucher for Rylaze.
- 12/18/2020: BLA 761179 accepted under the Real-Time Oncology Review pathway.
- 03/30/2021: A request for orphan designation for Rylaze in ALL and LBL was submitted.
- 04/30/2021: The submission of BLA 761179 was completed.
- 05/22/2021: Midcycle meeting was held.
- 06/22/2021: Wrap up meeting was held. The request for orphan designation was granted for treatment of ALL.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Acute lymphoblastic leukemia (ALL) is a malignancy characterized by bone marrow proliferation of immature lymphoid cells with spread to the circulating blood and other organs. The risk of this malignancy is highest in children younger than five years of age; the risk then decreases gradually until approximately the mid-twenties. The risk increases again after the age of 50 years of age with median age at diagnosis of 15 years. ALL is the most common type of childhood leukemia, accounting for around 80% in children but for only around 20% of leukemias in adults. Between 2001–2014, a total of 38,136 new pediatric ALL cases were diagnosed in the United States. Overall the incidence of ALL was 34.0 cases per 1 million. Rates were highest in children aged 1–4 years (75.2 per 1 million).[c,2] Among children with ALL, approximately 98% attain remission with treatment.[d] Approximately 85% of patients aged 1 to 18 years with newly diagnosed ALL treated on current regimens are expected to be long-term event-free survivors, with over a 90% five year survival rate.

Lymphoblastic lymphoma (LBL) is a type of Non-Hodgkins Lympoma, and is most often a malignancy of young adults. This type of cancer is fairly rare and aggressive; it is characterized by immature lymphoblasts. The rate of Non-Hodgkin lymphoma increases as people get older. With current treatments, the overall survival rate at 5 years in children with lymphoblastic lymphoma is 80-90%, and the overall survival rate in adults is 45-55%. Disease-free survival rates at five years range from 70% to 90% in children and from 45% to 55% in adults.[c,e,3] Although ALL and LBL are different types of blood cancer they are similar in terms of both malignancies consist of rapidly growing lymphoblasts and both require a treatment that targets these cells.

3.2 Description of Current Treatment Options

As described in section 2.1 of this review, the depletion of L-asparagine by L-asparaginase selectively kills cancer cells, making asparaginase products an important component of many induction protocols which aim to achieve complete remission. Most induction protocols consist of a glucocorticoid, vincristine, an asparaginase product, and optional use of an anthracycline.[4]

Most asparaginase products approved for treatment of ALL are derived from *E. coli*. The *E. Coli* – derived formulations include Elspar (approved in 1978; no longer available in the U.S.), Oncaspar (approved in 1994), and Asparlas (approved in 2018). Due to the bacterial source, asparaginases are highly allergenic and immunogenic. Allergic reactions can range from mild, local injection site reactions to severe anaphylaxis. Silent inactivation of asparaginase therapy occurs when circulating antibodies neutralize L-

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

asparaginase activity or it becomes rapidly cleared. Research supports that switching patients who develop hypersensitivity or inactivation to *E. coli*-derived asparaginase to the alternative non-*E. coli*-derived asparaginases can still achieve adequate treatment. The L-asparaginase , Erwinaze, (approved in 2011) is derived from from Erwinia chrysanthemi and is currently the only FDA-approved asparaginase indicated as part of the chemotherapeutic regimen for patients with ALL who have developed hypersensitivity to *E. coli*-derived asparaginase.[5] None of these drugs have a Boxed Warning or a REMS.

4 Benefit Assessment

The clinical development program for Rylaze included two studies: a completed phase 1 study in healthy adult participants (JZP458-101) designed to identify an effective starting dose and an ongoing pivotal phase 2/3 study (JZP458-201) in pediatric and adult patients with ALL/LBL who have developed hypersensitivity to *E. coli*-derived asparaginases.[6] The hypersensitivity was defined as an allergic reaction or silent inactivation.

The phase 1 study JZP458-101 was a randomized, single-center, open-label study to evaluate the safety, tolerability, and pharmacokinetics (PK) of a single dose of JZP-458 in 24 healthy adult participants via either intravenous (IV) infusion or IM administration. An Erwinaze dosing arm was also included. An IM dose of 25 mg/m^2 and IV dose of 37.5 mg/m^2 were studied. Serum asparaginase activity levels serve as a surrogate marker for asparagine depletion. A nadir serum asparaginase activity (NSAA) level ≥ 0.1 IU/mL is an acceptable threshold to demonstrate adequate asparagine depletion in clinical practice. Based on the phase 1 study data, population pharmacokinetic (PK) modeling, and simulations performed at the end of the study, the IM and IV dose were expected to achieve 72-hour NSAA levels ≥ 0.1 IU/mL in 100% of the whole population after IM administration, and 80.9% in adult or 94.5% in pediatric populations after IV administration. Based on the totality of the safety and PK data in this phase 1 study, the recommended phase 2/3 starting dose for the IM route of administration in cancer patients was 25 mg/m^2.

The primary efficacy endpoint of the pivotal phase 2/3 study was the response rate, defined as the proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL. This study was designed to assess the tolerability and efficacy of Rylaze by the serum asparaginase activity with additional supportive analyses for asparagine depletion and anti-drug antibody (ADA) levels. Six doses of Rylaze were substituted for each dose of a long-acting *E. coli*-derived asparaginase. Two consecutive weeks of treatment with Rylaze were defined as one course. Multiple courses could be administered as determined by each patient's particular treatment plan. This study consisted of two parts: Part A to determine the dose for IM administration and to confirm safety and efficacy; and Part B to define the optimal dose and schedule of IV therapy. At the time of BLA submission, a total of 86 patients were in the study; 33 patients at the 25 mg/m^2 dose Monday/Wednesday/Friday (MWF) for a total dose of 150 mg/m^2 per each course and 53 patients at the 37.5 mg/m^2 dose MWF for a total dose of 225 mg/m^2 per each course. There was an ongoing IM portion of the study for patients at 25/25/50 mg/m^2 dosing regimen MFW for a total dose of 200 mg/m^2 per each course.

The primary efficary endpoint was 72-hour proportion of participants who received at least one dose of Rylaze with at least one 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. At a dose of 25 mg/m^2 and 37.5 mg/m^2, the percentage of participants achieving NSAA levels ≥ 0.1 IU/mL at the last 48-hour assessment was 96.9% (95% Confidence Interval (CI): 90.8%, 100%) and 98.1% (95% CI: 94.5%, 100.0%), respectively. The lower bound of the 95% CI exceeds 90%, supporting the efficacy of 25 mg/m^2 and 37.5 mg/m^2 Ryalze dosing every 48-hours (See Table 1). At the last 72- hour assessment, the percentage of participants achieving NSAA levels ≥ 0.1 IU/mL at the in Course 1 was 65.5% (95% CI: 48.2%, 82.8%) and 80.4% (95% CI: 69.5%, 91.3%), respectively (See Table 1).

Table 1: Proportion of Participants with Last 72- and 48-hour NSAA Levels ≥ 0.1 IU/mL during the First Course of JZP-458 (Efficacy Analysis Set DCO October 14 2020)

NSAA Level	Time Point	IM 25 mg/m^{2}a (N = 33)			IM 37.5 mg/m^{2}a (N = 53)		
		N	n (%)	95% CI	N	n (%)	95% CI
≥ 0.1 IU/mL	Last 48-hour	32	31 (96.9)	90.8, 100.0	53	52 (98.1)	94.5, 100.0
	Last 72-hour	29	19 (65.5)	48.2, 82.8	51	41 (80.4)	69.5, 91.3

Abbreviations: CI = confidence interval; IM = intramuscular; NSAA = nadir serum asparaginase activity
a Doses were administered on a Monday, Wednesday, Friday schedule.
Percentages were calculated with the number of participants for each course and schedule as a denominator.
The Efficacy Analysis Set at 72-hour (primary efficacy endpoint) includes participants administered who received at least one dose of JZP 458 with at least one 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. The Efficacy Analysis Set at 48-hour (key secondary efficacy endpoint) includes participants who received at least one dose of JZP-458 with at least one 48-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1.
95% CI was calculated by the Wald method.

Source: Table 5, FDA BLA Multidisciplinary Review and Evaluation, BLA 76119 Rylaze (asparaginase erwinia chrysanthemi [recombinant]-rywn) injection, for IM use. Review in progress; accessed 6/21/2021.

The Review Team agreed with the Applicant that the data from the Study JZP458-201 simulation supports the proposed dosing regimens:[e]

- Preferred option: Rylaze mg/m^2 administered IM Mondays and Wednesdays and 50 mg/m^2 on Fridays for a total of six doses every two weeks. This is the preferred dosing regimen because it provides optimal benefit:risk profiles for Rylaze, with sustained NSAA levels ≥ 0.1 IU/mL over 48- and 72-hour dosing durations with acceptable safety to provide meaningful benefit to patients, and to allow for MWF dosing in line with current treatment practice.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

- The data also support Rylaze being given as 25 mg/m^2 administered IM every 48-hours for two weeks for a total of seven doses.

Refer to the FDA BLA Multidisciplinary Review and Evaluation: BLA 76119 Rylaze (asparaginase erwinia chrysanthemi [recombinant]-rywn) injection for more information.[7]

5 Risk Assessment & Safe-Use Conditions

Deaths and Serious Adverse Events

Safety data was compiled from the completed phase 1 study in healthy adult participants (JZP458-101) and the ongoing pivotal phase 2/3 study (JZP458-201) in pediatric and adult participants with ALL/LBL who have developed hypersensitivity to *E. coli*-derived asparaginases (allergic reaction or silent inactivation).[6]

There were no deaths or serious adverse events (SAEs) in phase 1 study in healthy adult participants (JZP458-101). There were also no deaths in JZP458-201 at the time of the BLA submission data lock, October 2020. However, by the time an updated data review was submitted in January 2021, there were three deaths in JZP458-201; all were attributed by the investigator to the participant's underlying disease or complications of multiagent chemotherapy for ALL/LBL. The study population is immunocompromised and receiving multi-agent/modal antineoplastic treatment, and there a high risk of mortality in this population.

As of October 2020, 31.4% of participants (27 of 86) experienced at least one SAE during the study. The most frequently reported SAE, occurring in at least three of 86 participants [3.5%] included febrile neutropenia (13 of 86 participants [15.1%]), stomatitis (4 of 86 participants [4.7%]), and pyrexia and dehydration (3 of 86 participants [3.5%] each). All of the SAEs that occurred were considered not related to study drug, except for events febrile neutropenia, pancreatitis drug hypersensitivity (2 of 86 participants [2.3%] each); and chills, pain, and headache (1 of 86 participants [1.2%] each).

Allergic Reactions (Including Hypersensitivity and Anaphylaxis)

In Study JZP458-201, allergic reactions, including hypersensitivity and anaphylaxis, occurred in 21 of 86 patients (24.4%). Six patients, or 7.0% had events considered related to study drug. All allergic reactions in these 6 participants were resolved. One patient with hypersensitivity was discontinued from the study.

Pancreatitis

As of the data cutoff for the BLA initial analysis (October 2020), 2 of 86 participants (3.8%) have experienced an event of ≥ Grade 3 pancreatitis that was considered related to the study drug and led to discontinuation of study drug.

Hepatotoxicity

Hepatic toxicity was observed in 15 patients (17.4%), with 9 (10.5%) assessed as related to Rylaze. Events related to hepatotoxicity were ALT increased (9.3% of participants [8/86]), AST increased (8.1% of participants [7/86]), and blood bilirubin increased (2.3% of participants [2/86]).

Thrombosis

Serious thrombotic events, have been reported following treatment with L-asparaginase class products; therefore, this was an adverse event of special interest. These events were not seen with Rylaze.

Hemorrhage

In patients treated with asparaginase class products, hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Bleeding was reported in 16% of patients treated with Rylaze, and it was considered severe in 1%.

6 Expected Postmarket Use

Rylaze will likely be used in both settings where cancer patients are treated, both inpatient and oupatient. The most likely prescribers for Rylaze will be oncologists, who should be familiar with the management of the adverse events known to be associated with treatment for ALL and LBL.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Rylaze beyond routine pharmacovigilance and labeling. The Applicant proposed describing the risks in the *Prescribing Information* sections for *Contraindications, Warnings and Precautions,* and *Patient Counseling Information*.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for Rylaze, the review team considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The safe use of Rylaze by experienced physicians can be managed through labeling as the benefits for patients with ALL/LBL outweigh potential risks associated with Rylaze.[f]

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug*

Based on the efficacy and safety information currently available, the clinical reviewers stated that Rylaze shows clinically meaningful benefit, and recommend approval as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL in adult and pediatric patients one month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

In the United States, ALL is the most common malignancy in children and adolescents. LBL is fairly rare but occurs in young adults, and is considered aggressive. Improvement and cure for these conditions is dependent on effective treatment. Both of these cancers require a multi-chemotherapeutic regimen with asparaginase as a necessary component of the regimen. Asparaginase formulations deriving from *E. Coli* are frequently associated with hypersentivity and there is a unmet need for additional asparaginases from non-bacteria sources. There is currently only one FDA-approved asparaginase (Erwinaze) indicated as part of the chemotherapeutic regimen for patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase. Furthermore, there is a shortage of this product.[7] As a result there is urgent need for additional asparaginases.

The expected benefit of Rylaze and safety profile are comparable to that of the currently approved asparaginase products. These risks are communicated through labeling and there are no Boxed Warning or REMS for these products. The likely prescribers for Rylaze will be oncologists who are specialized in the treatment of cancer patients and knowledgeable in managing the risk profile associated with asparaginase products. The risks identified are risks that these providers have encountered in their practice experience and can manage without additional risk mitigation measures beyond labeling.

DRM has determined that a REMS is not necessary to ensure the benefits of Rylaze outweigh its risks. The most concerning adverse reactions observed with the use of Rylaze are hypersensitivity, pancreatitis, thrombosis, hemorrhage and hepatotoxicity. The sections of *Contraindications and Warnings and Precautions* will be used to communicate the safety issues and management of toxicities associated with Rylaze, as well as information to be included in *Patient Counseling Information* to inform patients.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks of Rylaze. The management of the risks associated with Rylaze treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

10 References

[1] Jazz Pharmaceuticals. Proposed Prescribing Information for Rylaze, [June 22, 2021].

[2] Siegel DA, Henley SJ, Li J, Pollack LA, Van Dyne EA, White A. Rates and Trends of Pediatric Acute Lymphoblastic Leukemia — United States, 2001–2014. MMWR Morb Mortal Wkly Rep 2017;66:950–954. DOI: http://dx.doi.org/10.15585/mmwr.mm6636a3

[3] National Cancer Care Network. NCCN Clinical Guidelines in Oncology: Acute Lymphoblastic Leukemia, Version 2.2016. NCCN.org. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. March 12, 2018

[4] Hunger, S., Mullighan, C. N Engl J Med 2015; 373:1541-1552.

[5] Panosyan EH, Seibel NL, Martin-Aragon S, et al. Asparaginase antibody and asparaginase activity in children with higher-risk acute lymphoblastic leukemia: Children's Cancer Group Study CCG-1961. Journal of Pediatric Hematology/Oncology. 2004; 26:217-26.

[6] Jazz Pharmaceuticals. Clinical Overview, April 30, 2021.

[7] FDA BLA Multidisciplinary Review and Evaluation: BLA 76119 Rylaze (asparaginase erwinia chrysanthemi [recombinant]-rywn) injection, for IM use. Review in progress; accessed June 21, 2021.

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