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)

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Application Number	219685
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Reviewer Name(s)	Carla S.C. Darling, PharmD, BCPS
Team Leader(s)	Jacqueline Sheppard, PharmD
Acting Division Director	Laura Zendel, PharmD
Review Completion Date	August 26, 2025
Subject	Evaluation of Need for a REMS
Established Name	Rilzabrutinib
Trade Name	Wayrilz
Name of Applicant	Genzyme Corporation
Therapeutic Class	Kinase inhibitor
Dosage Form(s)	Oral tablet
Dosing Regimen	400 mg tablet, taken orally twice daily

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EXECUTIVE SUMMARY

This review documents the Division of Risk Management's (DRM) evaluation to determine if a risk evaluation and mitigation strategy (REMS) for the new molecular entity Wayrilz (rilzabrutinib) is necessary to ensure the benefits outweigh its risks. Genzyme Corporation (Applicant) submitted a New Drug Application (NDA) 219685 for rilzabrutinib with the proposed indication for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment. The applicant did not submit a proposed REMS or risk management plan with this application. This application is under review in the Division of Nonmalignant Hematology (DNH).

The benefits of rilzabrutinib were demonstrated in one adequate and well controlled trial and confirmatory evidence from an open-label dose-finding study. The pivotal trial demonstrated a statistically and clinically significant improvement in the primary end point of durable platelet response in subjects with insufficient response to previous treatment.

The safety profile for rilzabrutinib was favorable; there were no serious adverse events associated with rilzabrutinib that required REMS consideration. Labeling is sufficient for communicating potential serious adverse events including serious infections.

Based on the available safety and efficacy data, the DNH and the DRM determined that a REMS is not necessary to ensure the benefits of rilzabrutinib outweigh its risks. Prescribers are likely familiar with the potential risks of rilzabrutinib and other BTK inhibitors. Similar to other agents of its class, the potential risk of serious infections, hepatotoxicity, (b) (4) associated with rilzabrutinib will be communicated in the Warnings and Precautions section of the Prescribing Information. At the time of this review, final labeling, and post-marketing requirements were still under negotiation. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

1. Introduction

This review documents the Division of Risk Management's (DRM) evaluation of whether a Risk Evaluation and Mitigation Strategies (REMS) for the new molecular entity (NME), Wayrilz (rilzabrutinib), is necessary to ensure the benefits outweigh its risks. Genzyme Corporation (Applicant) submitted a New Drug Application (NDA) 219685 for rilzabrutinib with the proposed indication for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment.[1] This application is under review in the Division of Nonmalignant Hematology (DNH). The applicant did not submit a proposed REMS or risk management plan with this application.[2]

2. Background

2.1. Product Information

Rilzabrutinib, a NME,[a] is a Bruton's tyrosine kinase (BTK) inhibitor. Rilzabrutinib is proposed for the treatment of adult patients with persistent or chronic ITP who have had an insufficient response (b) (4) to a previous treatment.[1] Rilzabrutinib mediates its therapeutic effect for ITP through multiple mechanisms of action: 1) inhibition of B cell activation and 2) interruption of antibody-coated cell phagocytosis by FcγR in spleen and liver.[3] Rilzabrutinib is proposed as a 400 mg oral tablet, taken twice daily, in the outpatient setting. The anticipated duration of use for rilzabrutinib is for long-term treatment as the proposed indication is for persistent or chronic ITP.[b,2]

As of the time of this review, the FDA approved four oral BTK inhibitors and none are approved with a REMS or a boxed warning: ibrutinib (approved 2013, NDA 205552), acalabrutinib (approved 2017, NDA 210259), zanubrutinib (approved 2019, NDA 213217), and pirtobrutinib (approved 2023, NDA 216059).[4-7] FDA approved BTK inhibitors are indicated mainly for hematological malignancies among other indications. Across the class of BTK inhibitors, the following risks are identified in Section 5, Warnings and Precautions, of the Prescribing Information for these products: infection, hemorrhage, cardiac arrythmia/failure, hypertension, cytopenias, (second) malignancy, and hepatotoxicity.

Rilzabrutinib was granted orphan drug designation for treatment of ITP and fast track designation for the investigation of rilzabrutinib for the treatment of ITP. If approved, rilzabrutinib will be the first BTK inhibitor approved for the treatment of ITP. Rilzabrutinib is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219685 relevant to this review:

- 10/15/2018: Orphan-drug designation granted.
- 10/15/2020: Fast track designation granted.
- 08/29/2024: NDA 219685 submission for rilzabrutinib received.[8]
- 02/12/2025: A mid-cycle meeting held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there were no significant safety issues identified as of the time of the mid-cycle meeting.

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

[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

ITP is an acquired autoimmune disorder characterized by a low platelet count resulting from platelet destruction and impaired platelet production.[9] ITP can be an isolated primary condition, or it may be secondary to other conditions. The diagnosis of primary ITP remains one of exclusion and there is no accurate, definitive test to diagnose ITP. The clinical presentation of ITP can range from asymptomatic to severe bleeding. Bleeding events in patients with ITP can be unpredictable and can include bruising and petechiae in the setting of severe thrombocytopenia or can include more serious bleeding such as menorrhagia, epistaxis, gastrointestinal hemorrhage, hematuria, and intracranial hemorrhage.[c] Symptoms of ITP are primarily related to thrombocytopenia and bleeding including fatigue. Patients can also experience decreased quality of life related to restrictions on activities, anxiety due to the risk of bleeding, and the burden of treatment and monitoring. In the United States, annual incidence estimates of ITP in adults ranges from 3.3 to 12 per 100,000 persons.[10,11,d] The incidence rate is higher among females compared to males.

3.2. Description of Current Treatment Options

There is no cure for ITP. The goal of ITP treatment is to reach a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels.[12] First-line therapy for patients with platelet count <30 x 10^9/liter and asymptomatic or minor mucocutaneous bleeding includes corticosteroids with or without intravenous immune globulin (IVIg) or anti-D therapy.[9] Thrombopoietin receptor agonists (romiplostim, avatrombopag, and eltrombopag) and spleen tyrosine kinase inhibitor (fostamatinib) are FDA approved second-line therapies for patients with chronic ITP who had insufficient responses to corticosteroids, IVIg, or splenectomy. Additional second-line treatment options include splenectomy and rituximab (off-label).[9] While there are some treatment options for patients with ITP, treatment options are limited for patients who relapse or are refractory to available therapies.[12] See Appendix 10.2 for a summary of FDA-Approved therapies.

4. Benefit Assessment

The pivotal clinical trial supporting this application is study LUNA 3, also known as PRN1008-018 (NCT04562766), a 24-week phase 3, a randomized, double-blind, placebo-controlled, multicenter study with a 28-week open-label extension (OLE) followed by a long-term extension (LTE). The study evaluated

[c] 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.*

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

oral rilzabrutinib 400 mg twice daily in 133 adults (≥ 18 years of age) versus placebo (69 adults) with insufficient response to immunoglobulins, anti-D therapy, or corticosteroids for a 12 to 24-week period.

At the end of 12 weeks of treatment, subjects were assessed for platelet response based on platelet count and absence of rescue therapy. Platelet response was defined as either a) platelet count of ≥50,000/µL or b) platelet count between ≥30,000/µL and <50,000/µL and at least doubled from baseline at any time during the first 12 weeks. Absence of rescue medication was defined as absence of rescue medication use in the 4 weeks prior to the elevated platelet count that meets platelet response criteria. At the end of the 12-week period, subjects who responded to treatment would complete the blinded 24-week treatment period before entering the 28-week OLE. Subjects who did not respond could discontinue from the study or enter the 28-week the OLE period. Following the 28- week OLE, subjects who demonstrated a platelet response, defined as platelet counts ≥50,000/µL or ≥30,000/µL and at least doubled from baseline at ≥50% of the visits without receiving rescue therapy while on treatment during the last 8 weeks of the open label period, could continue rilzabrutinib treatment for a maximum of 12 months from the date of the last adult participant to enter the LTE period.

The primary endpoint was the proportion of subjects achieving durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 50,000/µL for ≥ two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy. The study met the primary efficacy endpoint of durable platelet response with a higher response in the rilzabrutinib group of 31 (23.3%) subjects [95% CI, 16.12% to 30.49%]) compared with the placebo group (0 participants).[e] The risk difference for the rilzabrutinib group versus placebo was 23.1% [95%CI, 15.95, 30.31], with a p-value <0.0001. The key secondary endpoints were tested in the prespecified hierarchical order, which resulted in significant differences in favor of rilzabrutinib.

Additional data was provided from the LTE in the LUNA 3 trial and a two part phase 1/2 study, LUNA 2, also known as PRN1008-010 (NCT03395210), which provide confirmatory evidence of effectiveness for rilzabrutinib based on the observed pharmacodynamic effects.[12] See the integrated review for rilzabrutinib for more details regarding the DNH's conclusions for evidence of effectiveness.

The review team concluded that the Applicant provided substantial evidence of effectiveness based on adequate and controlled trial and confirmatory evidence that support the benefits of rilzabrutinib to produce an increased and sustained platelet count in adult patients with ITP with insufficient response to previous treatment.[12]

5. Risk Assessment & Safe-Use Conditions

The safety of rilzabrutinib was evaluated in the phase 3 pivotal trial (LUNA 3) and the two-part phase 1/2 study, LUNA 2. The safety database consists of 202 participants from the controlled LUNA 3 trial

[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.*

including 133 adults who received at least one dose of the proposed dose of rilzabrutinib and 69 who received placebo.

Serious AEs (SAEs) occurred in 12 (9%) subjects receiving rilzabrutinib compared to 8 (12%) of subjects receiving placebo. SAEs reported in the rilzabrutinib group include infection, peripheral embolism, bleeding, hepatobiliary disorders, thrombocytopenia, and renal abscess.

Adverse reactions resulting in discontinuation of rilzabrutinib occurred in 3 subjects (6%) and each reaction occurred once (peripheral embolism, erythema nodosum, neutropenia, multi-joint pain, esophageal varices, hemorrhage hepatic enzyme increased, heartburn, headache, leg pain, pneumonia, abdominal discomfort, diarrhea, and nausea). Of these, pneumonia (*Aspergillus fumigatus*) was the only serious adverse reactions[f] (SAR) and the only death that occurred in the rilzabrutinib group. The subject was a 75-year-old white female with past medical history significant for chronic ITP and long-term corticosteroid use. The review team concluded that there is a possibility that rilzabrutinib may have been related to this participant's infection or progression of infection.[12] Overall, the review team determined that the safety profile of rilzabrutinib was generally consistent with other approved BTK inhibitors and possibly less toxic.

As a class, BTK inhibitors have been associated with arial fibrillation/cardiac arrhythmias, cytopenias (anemia and neutropenia), hemorrhage, infections, and hepatotoxicity.[13] There were no cases of rilzabrutinib-related hemorrhage. Anemia occurred less frequently in the rilzabrutinib-treated group than the placebo-treated group. Neutropenia (Grade 4) occurred in 1 (0.8%) subject treated with rilzabrutinib and in no subjects treated with placebo. There were no other instances of lower grade neutropenia reported. Serious infections, hepatotoxicity, and cardiac arrhythmias are further discussed below.

5.1. Serious Infections

In the LUNA 3 trial, fatal pneumonia was the only death that occurred. As mentioned above, the review team concluded that there is a possibility that rilzabrutinib may have been related to this participant's infection or progression of infection. Other serious infections [one each (0.8%)] included COVID-19 infection, wound infection, and one patient experienced urinary tract infection and kidney abscess. No serious infections occurred in the placebo treated group.[g] The review team determined that there is a possibility that rilzabrutinib may have been related to the occurrence and/or progression of these

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[g] 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.*

infections based on rilzabrutinib's mechanism of action and its ability to target cells involved in inflammation and autoimmunity.[12] The risk of serious infections will be communicated in Section 5, Warnings and Precautions of the Prescribing Information for rilzabrutinib.[3]

5.2. Drug Induced Liver Injury

BTK inhibitors have been associated with drug-induced liver injury. The risk varies across products within the class and may be related to differences in pharmacokinetic and pharmacodynamic properties and different mechanisms of liver injury. Labeling for this risk is included in Section 5, Warnings and Precautions, for all approved BTK inhibitors.

There were no cases of severe drug-induced liver injury or that met criteria for Hy's Law in the clinical trials. One subject with history of cirrhosis prior to enrollment met potential Hy's Law. The subject was a 74-year-old white male with chronic ITP, diabetes mellitus, hepatic cirrhosis, esophageal varices status post bleeding episode, obesity, and hypertension. On day 43, he discontinued rilzabrutinib due to Grade 4 bleeding esophageal varices. The review team concluded that the esophageal varices and hepatic enzyme elevations were related to hepatic cirrhosis and not related to rilzabrutinib.[12]

In the pivotal trial, 6 (4.5%) subjects experienced an increase in alanine aminotransferase (ALT) greater than the 1 time the upper limit of normal (ULN) compared to 1 participant who received placebo. In 5 of the 6 participants with elevated liver transaminases, concomitant adverse events were identified that temporally had potential to contribute to the liver transaminase elevations; including fatty liver and temporally associated fever, temporally associated diarrhea, temporally associated tonsilitis and upper respiratory symptoms. Liver transaminase elevations were not associated with an elevation in bilirubin (direct, indirect, or total) with exception of the participant with known cirrhosis.

No clinically significant differences in the pharmacokinetics of rilzabrutinib were observed based on mild hepatic impairment (Child-Pugh class A). Rilzabrutinib exposure (both Cmax and AUC) increased by approximately 4.5-fold in participants with moderate hepatic impairment (Child-Pugh class B). Patients with severe hepatic impairment (Child-Pugh class C) and CLCR <46 mL/min have not been studied.[12]

The review team concluded that there does not appear to be a significant signal of hepatotoxicity in participants who received rilzabrutinib.[12] Monitoring bilirubin and transaminases at baseline and as clinically indicated during treatment will be communicated in Section 2 of the Prescribing Information.[3] Avoiding rilzabrutinib in patients with moderate to severe liver impairment (Child-Pugh class B-C) will be communicated in Section 8. Because hepatotoxicity has been identified as a class risk for BTK inhibitors and the total population treated with rilzabrutinib is small, the review team recommends to convey the risk of hepatotoxicity in Section 5, Warnings and Precautions of the Prescribing Information for rilzabrutinib.[12]

5.3. Cardiac Arrythmias

BTK inhibitors have been associated with cardiac arrythmias. Labeling for the risk of cardiac arrythmias is included in Section 5, Warnings and Precautions for all approved BTK inhibitors. There were no cases of

atrial fibrillation and no grade 3 or 4 events were reported in the pivotal trial. (b) (4)

6. Expected Postmarket Use

The anticipated prescribing population for rilzabrutinib will be hematologists. These prescribers are likely familiar with the potential risks of serious infections, hepatotoxicity, and cardiac arrhythmias associated with rilzabrutinib and other approved BTK inhibitors. Rilzabrutinib is intended for self-administration by the patient or caregiver in the outpatient setting. If approved, rilzabrutinib will be the first FDA approved BTK inhibitor for the treatment of adult patients with persistent or chronic ITP who have had an insufficient response to immunoglobulins, anti-D therapy, or corticosteroids.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for rilzabrutinib beyond routine pharmacovigilance and labeling. The Applicant states that the overall benefit-risk assessment for rilzabrutinib is favorable and that "the potential risks are sufficiently mitigated with routine risk mitigation activities."[2] The Applicant does not propose a Boxed Warning in the labeling.[1]

8. Discussion of Need for a REMS

The review team recommends approval of rilzabrutinib based on the efficacy and safety information currently available.

If approved, rilzabrutinib would be the first BTK inhibitor treatment option for adult patients with persistent or chronic ITP who had an insufficient response to previous therapy. As there is no cure for ITP and treatment options are limited for patients who relapse or are refractory to available therapies; additional treatment options are needed for this patient population. Rilzabrutinib can provide another treatment option as the use of rilzabrutinib can produce an increased and durable platelet count in adults with ITP with insufficient response to previous therapies.

The review team determined that rilzabrutinib was safe and well tolerated at the proposed dose regimen for the treatment of adult patients with persistent and chronic ITP. There were no serious adverse events associated with rilzabrutinib that required REMS consideration. As there is a possibility that rilzabrutinib may be associated with the occurrence and/or progression of infections, the potential risk of serious infections will be communicated in Section 5, Warnings and Precautions of the Prescribing Information for rilzabrutinib. Although this drug class has been associated with drug-induced liver injury and cardiac arrhythmias, these risks are not anticipated to be a significant concern for rilzabrutinib. The risks of hepatotoxicity (b) (4) will be communicated in Section 5, Warnings and Precautions of the rilzabrutinib Prescribing Information.

As prescribers are likely familiar with the potential risks of rilzabrutinib and other agents of its class, this reviewer concluded that based on available safety information, a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for rilzabrutinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

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10.2. Table 1: Summary of FDA-Approved Drugs for the Treatment of ITP

Drug[14-17] **(Approval Date)**	**Indication**	**Dosing and Administration**	**Important Safety and Tolerability Issues**	**Risk Management Approaches**
Nplate – romiplostim (2008)	ITP in adults and pediatric patients 1 year of age and older with insufficient response to corticosteroids, immunoglobulins, or splenectomy	1 mcg/kg SC weekly; adjust by 1 mcg/kg weekly to achieve platelet count ≥ 50×10^9/liter as necessary to reduce the risk for bleeding	• Progression of myelodysplastic syndrome to acute myelogenous leukemia • Thrombotic/ thromboembolic complications • Worsening thrombocytopenia due to neutralizing antibodies or other causes	Labeling – Warnings and Precautions
Promacta – eltrombopag (2008)	Chronic ITP in adult and pediatric patients 1 year of age and older with insufficient response to corticosteroids, immunoglobulins, or splenectomy	Adult and Pediatric Patients 6 Years and Older: 50 mg PO daily; adjust by 25 mg within 1 to 2 weeks to achieve platelet count ≥ 50 × 109/liter as necessary to reduce the risk for bleeding Pediatric Patients 1 to 5 Years: 25 mg PO daily	• Hepatotoxicity • Thrombotic/ thromboembolic complications, cataracts, worsening thrombocytopenia after discontinuation	Labeling – Box Warning, Warnings and Precautions

Doptelet – avatrombopag (2018)	Chronic ITP in adults who have had an insufficient response to a previous treatment	20 mg PO daily; may increase to 40 mg daily based on platelet response	• Thrombotic/ thromboembolic complications	Labeling – Warnings and Precautions
Tavalisse – fostamatinib (2018)	Chronic ITP in adults with insufficient response to previous treatment	100 mg PO twice daily; may increase to 150 mg twice daily	• Hypertension • Hepatotoxicity • Diarrhea • Neutropenia • Embryo-Fetal toxicity	Labeling – Warnings and Precautions

SC – subcutaneous injection; PO – by mouth

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