CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209299Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	209299
PDUFA Goal Date	April 17, 2018
OSE RCM #	2017-757, 2017-759
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 14, 2017
Subject	Evaluation of Need for a REMS
Established Name	Fostamatinib
Trade Name	Tavalisse
Name of Applicant	Rigel
Therapeutic Class	Tyrosine kinase inhibitor
Formulation(s)	Tablets: 100 mg, 150 mg
Dosing Regimen	100 mg oral twice daily for 4 weeks, then 150 mg twice daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tavalisse (fostamatinib) is necessary to ensure the benefits outweigh its risks. Rigel Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 209299 for fostamatinib with the proposed indication for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. The serious risks associated with fostamatinib include hypertension, liver toxicity, gastrointestinal toxicity, neutropenia, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Although responses to ITP treatment with glucocorticoids, intravenous IVIG, splenectomy, and thrombocytopenic receptor agonists may be encouraging, approximately one-third of patients remain severely thrombocytopenic for long durations and subject to the risk of spontaneous or trauma - induced hemorrhage. There remains a clear medical need to develop a new therapy for the treatment of refractory ITP. The risks of fostamatinib are manageable with appropriate monitoring and dose adjustments and, if approved, will be communicated in the Dosage and Administration and Warnings and Precautions sections of the product label. Additionally, if approved, the label will include a recommendation for a reduction (b) (4) if fostamatinib is used concomitantly with a strong CYP3A inhibitor. DRISK and the Division of Hematology Products (DHP) agree that a REMS is not needed to ensure the benefits of fostamatinib outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tavalisse (fostamatinib) is necessary to ensure the benefits outweigh its risks. Rigel Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 209299 for fostamatinib with the proposed indication for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Fostamatinib, a NME,[a] is a kinase inhibitor proposed for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Fostamatinib proposed as 100 mg and 150 mg tablets orally twice daily. Discontinue fostamatinib after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding. [b] Fostamatinib is not currently approved in any jurisdiction.

[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.*

Fostamatinib has demonstrated activity against spleen tyrosine kinase (SYK). The SYK is an important signaling molecule in the immune process that leads to platelet destruction in ITP. Fostamatinib prevents platelet destruction by inhibition of SYK signaling.

2.2 REGULATORY HISTORY

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

- August 25, 2015: Orphan drug designation granted.
- April 5, 2016: pre-NDA meeting held
- April 17, 2017: NDA 209299 submission received
- September 28, 2017: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for fostamatinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Immune thrombocytopenia (ITP) is a disorder manifested by immune mediated platelet destruction. ITP may be primary or secondary to a variety of conditions, including generalized autoimmune disease (as in systemic lupus erythematosus), lyphomatous disease, or chronic viral diseases (as in hepatitis and HIV). The diagnosis of primary ITP remains one of exclusion. There is no accurate, definitive test to diagnose ITP. In adults, primary ITP constitutes approximately 80% of the diagnosed patients, whereas the remaining 20% are affected by secondary ITP. Primary ITP has a prevalence of up to 9.5 per 100,000 adults and an incidence of about 3.3/100,000 adults per year,[c] and this increases with age.[1] Adult patients with ITP are far more likely to progress to a chronic course of the disease than pediatric patients; only 15% of adult patients undergo remission within 1 year after disease onset. Not all patients with chronic ITP need therapy. The major goal for treatment of ITP is to provide a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels. The overall risk of bleeding in ITP is low; it is greatest in individuals with platelet counts < 10,000/microL. Life-threatening bleeding is rare, but hemorrhagic deaths have been reported. Sites of severe bleeding include intracerebral (about 0.2%), gastrointestinal, and a variety of mucosal surfaces.[d] The mortality of ITP is considered to be similar to, or only marginally higher than, an age-matched population, despite the possibility of fatal hemorrhage or infection in the setting of therapies that cause immunosuppression.[2]

[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.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

First-Line therapies – The most commonly used agents for initial treatment of ITP for those who require it are glucocorticoids and intravenous immune globulin (IVIG).

Second-line therapies – There are 2 principal choices of second-line: splenectomy and rituximab. Thrombopoietin (TPO) receptor agonists are typically used when splenectomy and/or rituximab fail to produce a safe platelet count. The table in Appendix 1 lists treatment options relevant to the proposed indication.

4 Benefit Assessment

Fostamatinib was studied in two identical randomized, placebo-controlled studies (referred to as FIT 1 and FIT2. FIT 1 (N=76) and FIT 2 (n=74) enrolled patients with chronic ITP, who had an insufficient response to previous treatment which included corticosteroids, immunoglobulins, splenectomy, and/or a thrombopoietin receptor agonist. The FIT 2 trial did not demonstrate a statistically significant difference between treatment arms, so only the results of the FIT 1 trail are described below.

In the randomized studies, patients were randomized 2:1 to fostamatinib (N=51) or placebo (N=25) for 24 weeks; randomization was stratified with respect to prior splenectomy and severity of thrombocytopenia. Stable concurrent ITP therapies (glucocorticoids, < 20 mg prednisone equivalent per day, or azathioprine) were allowed, and rescue therapy was permitted.

The primary endpoint is stable platelet response by week 24 (defined as achieving platelet count of ≥50,000/mcL on at least 4 of the last 6 visits between week 14-24). Patients who discontinue treatment prior to week 24 due to lack of efficacy or adverse event, or who receive rescue therapy after 10 weeks, were considered non-responders. In FIT 1 trial, nine patients (17.7%) in the fostamatinib arm achieved stable platelet response versus none of patient in the placebo arm (p=0.03).

The clinical review team concluded that fostamatinib demonstrated a marginal efficacy to treat patients with chronic ITP who have had an insufficient response to a previous therapy. [e3]

5 RISK ASSESSMENT [4]

Fostamatinib was studies in 2 double-blind, placebo-controlled trials, FIT 1 and FIT 2. The data reflected exposure to fostamatinib in 102 previously treated patients with chronic ITP. There were 3 deaths in the fostamatinib arm, one was due to plasma cell myeloma, one was due to sepsis, and one was due to anoxic encephalopathy (cardiopulmonary arrest secondary to congestive heart failure). There was one

[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.*

death due to sepsis reported in the placebo arm. Serious adverse reactions, described below, were hypertension, liver toxicity, gastrointestinal (GI) toxicity, neutropenia, and embryo-fetal toxicity.[f]

- Hypertension: Hypertension, including hypertensive crisis, can occur with fostamatinib therapy. There were 28% of patients in the fostamatinib arm who experienced hypertension compared to 13% of patients in the placebo arm.

- Liver toxicity: Elevated liver function tests, mainly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were reported in (b) (4)% of patients treated with fostamatinib compared to none of patients in the placebo arm. No patients met the criteria for Hy's Law. There were 5 patients whose ALT/AST>=5 x upper limits of normal (ULN). In all patients, levels returned to normal after holding/dose reduction/discontinuation. There was 1 patient whose ALT>=10 x ULN, AST>5 x ULN and levels returned to normal.

- The most common GI toxicities were diarrhea ((b) (4)% vs. 15%), nausea (19% vs. 8%), and abdominal pain (6% vs. 2%).

- Neutropenia (6% vs. 0%), including febrile neutropenia, can occur with fostamatinib therapy. One patient was hospitalized for fever accompanying neutropenia, and following discharge, resumed fostamatinib at a lower dose.

- Embryo-fetal toxicity: based on findings from animal studies and its mechanism of action, fostamatinib can cause fetal harm when administered to a pregnant woman.

If fostamatinib is approved, these serious risks will be communicated in the Warnings and Precautions section of the product label; additionally, the label will also include dose modification recommendations for these risks, as well as a recommendation for a dose modification (b) (4) if fostamatinib is used concomitantly with a strong CYP3A inhibitor.

6 Expected Post-Market Use

It is expected that hematologists/oncologists will be the primary prescribers and the use will be primarily in the outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for fostamatinib beyond routine pharmacovigilance and labeling.

[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.*

8 Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the clinical reviewers recommend approval of fostamatinib.

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for fostamatinib, DRISK considers patient population size, seriousness of the disease, expected benefit of the drug, the expected duration of treatment, and the seriousness of known or potential adverse reactions.

In adults, primary ITP constitutes approximately 80% of the diagnosed patients, whereas the remaining 20% are affected by secondary ITP. Primary ITP has a prevalence of up to 9.5 per 100,000 adults and this increases with age. Adult patients with ITP are far more likely to progress to a chronic course of the disease than pediatric patients; only 15% of adult patients undergo remission within 1 year after disease onset. Not all patients with chronic ITP need therapy. The major goal for treatment of ITP is to provide a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels. Life-threatening bleeding is rare, but hemorrhagic deaths have been reported. Sites of severe bleeding include intracerebral (about 0.2%),[5] gastrointestinal, and a variety of mucosal surfaces.

In FIT 1, a placebo-controlled clinical trial with 51 patients in the fostamatinib and 25 patients in the placebo arm, nine patients (17.7%) in the fostamatinib arm achieved stable platelet response versus none of patient in the placebo arm (p=0.03). The clinical review team concluded that fostamatinib demonstrated a marginal efficacy to treat patients with chronic ITP who have had an insufficient response to a previous therapy.

The serious risks of fostamatinib are hypertension, liver toxicity, GI toxicity (diarrhea, nausea or abdominal pain), neutropenia, and embryo-fetal toxicity. The recommendations for monitoring blood pressure, liver function tests, development of GI toxicity, and absolute neutrophil count (ANC) will be communicated in the Warnings and Precautions section of the labeling if the product is approved. To mitigate these risks, the proposed label will also include recommended dose modifications for those adverse reactions. Additionally, the label will include a recommendation for a dose modification (b) (4) if fostamatinib is used concomitantly with a strong CYP3A inhibitor.

Fostamatinib will likely be prescribed by hematologists/oncologists who should be familiar with these risks and how to manage them.

Although responses to glucocorticoids, intravenous IVIG, splenectomy, and thrombocytopenic receptor agonists may be encouraging, approximately one-third of patients remain severely thrombocytopenic[10] for long durations and subject to risk of spontaneous or trauma induced hemorrhage. There remains a clear medical need to develop a new therapy for the treatment of refractory ITP. The risks of serious adverse reactions are manageable and communicated in the proposed prescribing information. DRISK and DHP agree that a REMS is not necessary to ensure the benefits outweigh the risks of fostamatinib.

9 Conclusion & Recommendations

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

10 Appendices

Appendix 1: Summary of Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic)	Indication	Administration	Important Safety and Tolerability Issues	Risk Management Approaches
Glucocorticoids	1st Line	Oral or Intravenous	Toxicities of cardio-renal, endocrine, ophthalmic, & infections	Warnings
Intravenous immune globulin	1st Line	Intravenous	Thrombosis, renal dysfunction, acute renal failure or death	A Boxed warning
Rh_o (D) immune globulin	1st Line for pt who has an Rh^+ blood type & no splenectomy	Intravenous	Intravascular hemolysis (IVH), can lead to severe anemia, renal failure, multi-organ failure, & death	A Boxed warning
Splenectomy	2nd Line	Surgery	Complications of surgery, increased susceptibility to infection & vascular events	
Rituximab	2nd Line	Intravenous	Fatal infusion reactions, severe mucocutaneous reactions, hepatitis B reactivation, progressive multifocal leukoencephalopathy (PML)	A Boxed warning
Romiplostim (Nplate), a thrombopoietin receptor agonist	2nd Line, after splenectomy/ rituximab	Subcutaneous injection once weekly	Increases risk of progression to acute myelogenous leukemia in pt with MDS., Thrombotic complications, and possible formation of neutralizing antibodies.	Not a boxed warning; in section of Warnings & Precautions
Eltrombopag (Promacta), a thrombopoietin receptor agonist	2nd Line, after splenectomy/ rituximab	50 mg tablet oral once daily	In pts with chronic hepatitis C, may increase risk of hepatic decompensation if use with interferon & ribavirin	A Boxed warning; Warnings & Precaution: increased risk of thrombosis

10.1 REFERENCES

[1] George JN, Arnold DM, Immune thrombocytopenia in adults: initial treatment and prognosis, UpToDate, accessed September 7, 2017

2 George JN, Arnold DM, Immune thrombocytopenia in adults: Second-line and subsequent therapies, UpToDate, accessed September 7, 2017

[3] Lee, HZ. and Karuri, S. DHP, Mid-Cycle Clinical and Biostatistics presentation for fostamatinib (NDA 209299), September 15, 2017

[4] Proposed Prescribing Information for fostamatinib (NDA 209299), updated October 19, 2017.

5 Zufferey A, Kapur R, Pathogenesis and Therapeutic Mechanisms in Immune Thrombocytopenia (ITP). J Clin Med. 2017 Feb; 6 (2):16.

6 WinRh$_0$ Prescribing Information, dated January 2011.

7 Romiplostim Prescribing Information, dated June 2017.

8 Eltrombopag Prescribing Information, dated August 2015.

9 Rituximab Prescribing Information, dated April 2016.

10 Mazza P, Minoia C, et al. The use of thrombopoietin-receptor agonists in ITP. Ann Hematol 2016 95(2):239-244

11 Privigen - human immunoglobulin g liquid Prescribing Information, dated September 2017.

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/s/

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12/14/2017

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