CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210238Orig1s000

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	210238
PDUFA Goal Date	May 18, 2018
OSE RCM #	2017-2158
Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 26, 2018
Subject	Evaluation of Need for a REMS
Established Name	avatrombopag
Trade Name	Doptlet
Name of Applicant	Eisai Inc.
Therapeutic Class	Thrombopoietin (TPO) receptor agonist
Dosing Regimen	Based on the patient's baseline platelet count: $<40 \times 10^9$/L 60 mg once daily for 5 days; ≥ 40 to $<50 \times 10^9$/L 40 mg once daily for 5 days.

Table of Contents

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 (NME) Doptelet (avatrombopag) is necessary to ensure the benefits outweigh its risks. Eisai Inc., submitted a New Drug Application (NDA 210238) for avatrombopag, a thrombopoietin (TPO) receptor agonist, with the proposed indication for the treatment of thrombocytopenia (platelet count <50x10^9/L) in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. Treatment with avatrombopag should be started 10-13 days prior to the procedure. The risks associated with avatrombopag include thrombotic/thromboembolic events. The Applicant did not submit a proposed REMS or risk management plan with this application.

Nplate and Promacta are also thrombopoietin (TPO) receptor agonists which required a REMS at the time of their approval in 2008. The REMS for these drugs was originally approved with a Medication Guide (MG), elements to assure safe use (ETASU), an implementation system, and timetable for assessments, to mitigate the increased risks of hepatotoxicity, bone marrow fibrosis, serious hemorrhage resulting from worsened thrombocytopenia, and an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS). The REMS for Promacta was released in 2014, while the REMS for Nplate currently remains as a communication plan, after its modification in 2011 removing the MG and ETASU.

However, unlike Nplate and Promacta where treatment is indicated on a chronic basis, avatrombopag does not carry these risks, due to shorter duration of treatment (5 days). Based on this information, this DRISK reviewer's recommendation is that a REMS is not necessary to ensure the benefits of avatrombopag outweigh its risk.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME Doptelet (avatrombopag) is necessary to ensure the benefits outweigh its risks. Eisai Inc., submitted an NDA 210238 for avatrombopag with the proposed indication for the treatment of thrombocytopenia (platelet count <50x10^9/L) in adult patients with chronic with chronic liver disease who are scheduled to undergo a procedure. 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

Avatrombopag is a thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia (platelet count <50 x 10^9/L) in adult patients with chronic liver disease who are scheduled to undergo a procedure. This drug is not being proposed to be used chronically to normalize platelet counts and has not been studied as such.

Avatrombopag stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased production of platelets. Avatrombopag does not compete with TPO for binding to the TPO receptor and therefore, has an additive effect with TPO on platelet production.[1] Avatrombopag is available as 20 mg tablets with the recommended dose based on the patient's platelet count prior to a scheduled procedure as follows[1]:

Platelet Count ($x10^9$/L)	Once Daily Dose	Duration
<40	60 mg	5 days
≥40 to <50	40 mg	5 days

Dosing should begin 10 to 13 days prior to a scheduled procedure, and should be taken orally, once daily for 5 consecutive days.[a] The intended setting in which the drug is likely to be administered is in an outpatient setting.

Nplate and Promacta are also TPO receptor agonists, currently on the market, and the approved indications are included in Table 1. In the clinical trials Nplate was administered for extended time periods, in some patients up to 96 weeks and Promacta for at least a year.

Table 1

Drug	**Approved indications**
Promacta[2]* (eltrombopag)	• treatment of thrombocytopenia in ratients with chronic ITP • treatment of thrombocytopenia in patients with hepatitis C infection • treatment of severe aplastic anemia
Nplate[3]* (romiplostim)	• treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, splenectomy.
* Limitation Use: Promacta and Nplate are not indicated for the treatment of thrombocytopenia patients with myelodysplastic syndromes (MDS)	

Both Promacta and Nplate were approved with REMS in 2008 to mitigate the increased risks of hepatotoxicity, bone marrow fibrosis, serious hemorrhage resulting from worsened thrombocytopenia, and an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS). The REMS for Promacta and Nplate were originally comprised of a Medication Guide (MG), elements to assure safe use (ETASU), an implementation system, and timetable for assessments (approved in 2008). In 2011, these REMS were modified to remove the MG, ETASU, and implementation system, and to add a communication plan (CP) At that time, FDA concluded that establishing the long-term safety data in regards to the above risks for Nplate and Promacta would be best achieved through ongoing clinical trials, post-approval studies, and post-marketing adverse events reports. Thus, it was determined that the ETASU requirements related to safety data collection were not informative and were no longer necessary to ensure that the benefits of

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

outweighed its risks.[4,5] The CP REMS for Promacta was released in 2014. The CP REMS for Nplate currently remains though all communication activities have been completed. Labeling for Promacta contains a Boxed Warning for severe and potentially life threatening hepatoxicity in patients with Hepatitis C, and Nplate does not include any Boxed Warnings. Labeling discussions are ongoing but at this time for avatrombopag the proposed labeling does not include a Boxed Warning.

Avatrombopag is an NME,[b] and is under Priority Review. Avatrombopag is currently not marketed in any other jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210238 relevant to this review:

- 10/23/2017: NDA 210238 for avatrombopag received
- 01/09/2018: A Post 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 avatrombopag
- 05/21/2018: Prescription Drug User Fee Act (PDUFA) goal date

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Thrombocytopenia is a common complication in patients with CLD, and often worsens with the severity of disease. TPO, the principal physiologic regulator of platelet production is produced in the liver, circulates in the bloodstream, and delivered to the bone marrow where hematopoietic cells take place.[6] In patients with CLD, TPO production is decreased, often significantly, which results in decreased platelet production and thrombocytopenia. Clinical management of these patients can be challenging because they require several invasive diagnostic and therapeutic procedures over the course of their disease (sometimes averaging 3 per year), with each carrying the risk of significant bleeding due to the nature of their disease.[6]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Current the standard of care for patients with chronic liver disease to treat thrombocytopenia who are undergoing a procedure are platelet transfusions. Additional options for this patient population include splenectomy, splenic artery embolization, and trans jugular intrahepatic portosystemic stent shunting.[6] These procedures can result in risks such as infections, transfusion reactions, and the development of platelet refractoriness, which may increase the risk for complications such as spontaneous bleeding and secondary varices and coagulopathies.[6] If approved, avatrombopag would be the first drug to treat thrombocytopenia in this patient population prior to a scheduled procedure.

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

4 Benefit Assessment

The effectiveness of avatrombopag for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was established in 2 identically-designed multicenter, randomized, double-blind, placebo-controlled trials(ADAPT-1andADAPT-2). In each study, patients were assigned to the Low Baseline Platelet Count Cohort (<40 X 10^9L) or the High Baseline Platelet Count Cohort (≥40 to <50 X 10^9 L) based on their platelet count at baseline. Patients were then randomized in a 2:1 ratio to either avatrombopag or placebo. Four-hundred and thirty patients with CLD and thrombocytopenia received either avatrombopag (n=274) or placebo (n=156) daily for 5 days prior to a scheduled procedure, and had 1 post-dose safety assessment. Patients were divided into two groups based on their mean platelet count at baseline. The majority of patients were males (65%) and median subject age was 58 years (ranging from 19-86 years of age). The racial and ethnic distribution was White (60%), Asian (33%), Black (3%), and Other (3%).[1]

In both baseline platelet count cohorts, patients in the avatrombopag treatment groups had a greater proportion of responders than the corresponding placebo treatment groups that was both clinically meaningful and statistically significant.

In addition, both trials demonstrated a higher proportion of patients who achieved the target platelet count of ≥ 50 x 109/L on the day of the procedure, a secondary efficacy endpoint, in both avatrombopag-treated groups versus the placebo-treated groups for both cohorts (Low Baseline Platelet Count Cohort-ADAPT-1: 69% vs 4%, respectively; P <0.0001;ADAPT-2: 67% vs 7%, respectively; P <0.0001; High Baseline Platelet Count Cohort- ADAPT-1: 88% vs 21%, respectively; P <0.0001; ADAPT-2: 93% vs 39%, respectively; P <0.0001). Furthermore, both trials demonstrated a greater mean change in platelet counts from baseline to the day of the procedure, a secondary efficacy endpoint, in both avatrombopag-treated groups versus the placebo-treated groups for both cohorts (Low Baseline Platelet Count Cohort-ADAPT-1: 32.0x109/L vs 0.8x109/L, respectively; P <0.0001;ADAPT-2: 31.3x109/L vs 3.0x109/L, respectively; P <0.0001; High Baseline Platelet Count Cohort-ADAPT-1: 37.1x109/L vs 1.0x109/L, respectively; P <0.0001;ADAPT-2: 44.9x109/L vs 5.9x109/L, respectively; P <0.0001).[1]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for avatrombopag. This safety information is from the Applicant's registrational trials, ADAPT-1 and ADAPT-2 which are described above. Thrombotic and thromboembolic events is a risk of avatrombopag which will be communicated in Warnings and Precautions of the Prescribing Information. There are no other major risks of avatrombopag that are described in the label at this time.

5.1 THROMBOTIC/THROMBOEMBOLIC EVENTS

Due to the mechanism of action, TPO receptor agonists have been associated with thrombotic and thromboembolic complications, including portal vein thrombosis in patients with CLD. There was one event of portal vein thrombosis in a patient treated with avatrombopag in the clinical trial.

Recommendations are to consider the potential increased thrombotic risk when administering avatrombopag to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions such as Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency.[1,c]

6 Expected Postmarket Use

Avatrombopag will be dispensed in an outpatient care setting, limited to when the patient is scheduled to undergo a procedure within 5 to 8 days after the last dose of avatrombopag. Treatment is limited to 10-13 days prior to the planned procedure.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

Currently, the standard of care for patients with CLD to treat thrombocytopenia who are undergoing a procedure are platelet transfusions, and other medical procedures that may significantly increase bleeding risks as well as other complications. There is currently no pharmacotherapeutic treatment options approved for this patient population, with the proposed indication for the treatment of thrombocytopenia (platelet count < 50 x 10^9/L) in adult patients with chronic liver disease who are scheduled to undergo a procedure.

Avatrombopag is a TPO receptor agonist like the currently approved drugs Nplate and Promacta, in which a REMS was originally required as part of their approval. These drugs are approved with several indications, in chronic use as noted above in Table 1. However, unlike Nplate and Promacta, avatrombopag is only being indicated for short term use; dosing should be started 10-13 days prior to the patient's planned procedure and administered for only 5 consecutive days. Because of the short term use of avatrombopag, the risk profile is different than Nplate and Promacta. Thrombotic complications are the only common adverse events that are noted in the labels for Nplate, Promacta and avatrombopag. The other adverse events noted in the Nplate and Promacta label such as hepatoxicity, and increased risk of death and progression of myelodysplastic syndromes to Acute Myeloid Leukemia is not in the avatrombopag label. Based on this information, this DRISK reviewer's recommendation is that a REMS is not necessary to ensure the benefits of avatrombopag outweigh its

[c] 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 adrug.*

risk. The Clinical Reviewer recommends approval of avatrombopag based on the efficacy and safety information currently available.

9 Conclusion & Recommendations

The DRISK and DHP agree that the benefit-risk profile for avatrombopag is favorable, therefore a REMS is not necessary for avatrombopag to ensure the benefits outweigh the 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 so that this recommendation can be reevaluated.

10 References

[1] Doptlet draft Prescribing information, February 7, 2018

[2] Promacta Prescribing Information, Novartis Pharmaceuticals Corporation, Revised October 2017

[3] Nplate Prescribing Information, Amgen, Revised October 2017

[4] Robottom S. REMS Modification review to eliminate ETASU for Nplate. November 17, 2011

[5] Robottom S. Review to determine if the communication plan REMS for Promacta can be released. July 1, 2014

[6] Maan R et al. Management of thrombocytopenia in chronic liver disease: focus on pharmacotherapeutic strategies. Drugs. 2015;75(17):1981-92

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAOMI B REDD
02/27/2018

CYNTHIA L LACIVITA
02/27/2018