CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210923Orig1s000

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	210923
PDUFA Goal Date	August 26, 2018
OSE RCM #	2017-1980; 2017-1983
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	May 23, 2018
Subject	Review to determine if a REMS is necessary
Established Name	Lusutrombopag
Trade Name	Mulpleta
Name of Applicant	Shionogi, Inc.
Therapeutic Class	Thrombopoietin receptor agonist
Formulation(s)	3 mg tablet
Dosing Regimen	One 3-mg tablet taken orally once daily with or without food for 7 days

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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 lusutrombopag (Mulpleta), a thrombopoietin (TPO) receptor agonist, is necessary to ensure the benefits outweigh its risks. Shionogi, Inc. submitted a New Drug Application (NDA) 210923 for lusutrombopag with the proposed indication as treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are at increased risk for bleeding associated with invasive procedures. The risks associated with lusutrombopag include thrombotic and thromboembolic complications. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Information.

Nplate and Promacta are 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. Avatrombopag, a TPO receptor agonist, was approved on May 22, 2018 without a REMS , it is indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. Similar to avatrombopag, lusutrombopag does not carry the same risks associated with Nplate and Promacta due to shorter duration of treatment (7 days).[1]

DRISK and Division of Hematology Products (DHP) agree that if approved, a REMS is not necessary to ensure the benefits of lusutrombopag outweigh its risks. Current treatment options for thrombocytopenia in CLD have been platelet transfusions, splenic artery embolization, splenectomy, and TIPS placement, which are associated with multiple limitations and complications. Treatment options are limited, atrombopag is the only therapy currently approved for this indication. In the clinical trial, lusutrombopag appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reaction associated with the use of lusutrombopag is thrombotic and thromboembolic complications; this risk and recommended guidance to manage toxicities, will be communicated in the Warnings and Precautions section of the product label. The Warnings and Precautions section of the label also instructs prescribers that lusutrombopag should not be administered to patients with CLD in an attempt to normalize platelet counts.

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) lusutrombopag (Mulpleta) is necessary to ensure the benefits outweigh its risks. Shionogi, Inc. submitted a New Drug Application (NDA) 210923 for lusutrombopag with the proposed indication as treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are at increased risk for bleeding associated with invasive procedures.[2] This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Information.

2 Background

2.1 PRODUCT INFORMATION

Lusutrombopag is a NME NDA type 505(b)(1) pathway application.[a] It is a thrombopoietin (TPO) receptor agonist proposed as a treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with invasive procedures. Lusutrombopag is an orally bioavailable, small molecule TPO receptor agonist that interacts with the transmembrane domain of human TPO receptors expressed on megakaryocytes to induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation. Lusutrombopag is prepared as 3 mg tablet to be taken by the oral route.[2,3] The proposed dose of lusutrombopag is one 3-mg tablet taken orally once daily with or without food for 7 days.[b] Lusutrombopag was granted a fast track designation on March 6, 2017. Lusutrombopag has been marketed in Japan since December 1, 2015.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for lusutrombopag (NDA 210923) relevant to this review:

- 01/08/2009: Investigation New Drug (IND) 104047 submission was received.
- 03/06/2017: Fast track designation granted.
- 05/12/2017: Applicant informed at pre-NDA meeting that the need for a REMS for lusutrombopag will be made upon reviewing the NDA.
- 12/26/2017: NDA 210923 submission for lusutrombopag with the proposed indication for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with invasive procedures, received.
- 04/13/2018: 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 lusutrombopag. The Agency requested to provide a copy of the Applicant's risk management plan as it becomes available.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Thrombocytopenia is the most common hematological abnormality encountered in patients with CLD, occurring in 64%–84% of patients with cirrhosis or fibrosis.[4,c] In patients with CLD or chronic hepatitis C

[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*

[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.*

virus (HCV), the pathogenesis of thrombocytopenia is multifactorial. Possible causes include splenic sequestration of platelets, suppression of platelet production in the bone marrow, and decreased activity of the hematopoietic growth factor TPO.[5] TPO, the principal physiologic regulator of platelet production is produced in the liver, circulates in the bloodstream, and is delivered to the bone marrow where hematopoietic cell growth takes place. In patients with CLD, TPO production is decreased, often significantly, which results in decreased platelet production and thrombocytopenia. Thrombocytopenia frequently complicates the management of patients with CLD who require treatment for their underlying disease or who must undergo an invasive procedure because it carries the risk of significant bleeding due to the nature of their disease.[6,d]

3.2 Description of Current Treatment Options

Traditionally, the treatment options for thrombocytopenia in CLD have included platelet transfusions, splenic artery embolization, splenectomy, and Transjugular Intrahepatic Portosystemic Stent (TIPS) placement.[7] There are no international consensus guidelines that currently define the threshold platelet count below which platelet transfusion is needed prior to invasive procedures in this patient population.[6] Thus, clinicians may rely on local guidelines, which recommend prophylactic administration of platelets to achieve a platelet count ≥ 50,000/μL prior to many invasive procedures.[8] While these treatment options often effectively increase the platelet count, costs and risks are substantial. Platelet transfusions are also associated with multiple limitations and complications. Platelet counts may fail to adequately rise post transfusion; platelets do not always ensure a hemostatic platelet level, especially in patients with a high risk of bleeding.[9] Despite being the most effective option, patients can become refractory to multiple transfusions due to human leukocyte antigen alloimmunization. Moreover, it is associated with the development of febrile nonhemolytic reactions and transfusion-related infections.[6] Avatrombopag is the only TPO receptor agonist, approved for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.[14]

4 Benefit Assessment

The efficacy of lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was evaluated in 2 randomized, double-blind, placebo-controlled trials, L-PLUS 1 (N=97) and L-PLUS 2 (N=215). Patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50×10^9/L were eligible to participate. Patients were randomized 1:1 to receive 3 mg of lusutrombopag or placebo once daily for up to 7 days. Randomization was stratified by liver ablation/coagulation or other procedures and the platelet count at screening/baseline. In L-PLUS 1, 57% of patients underwent procedures other than liver ablation/coagulation and 43% underwent liver ablation/coagulation (RFA/MCT). In L-PLUS 2, 98% of patients underwent procedures other than liver ablation/coagulation and 2% underwent liver ablation/coagulation (RFA/MCT).

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for lusutrombopag. In L-PLUS 1, the major efficacy outcome was the proportion of patients who require no platelet transfusion prior to the primary invasive procedure. In L-PLUS 2, the major efficacy outcome was the proportion of patients who require

[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.*

no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding (i.e. platelet preparations, other blood preparations, including red blood cells and plasma, volume expanders) from randomization through 7 days after the primary invasive procedure.[2,11] In both trials, additional efficacy outcomes included the proportion of patients who require no platelet transfusion during the study, proportion of responders, duration of the increase in platelet count defined as the number of days during which the platelet count was maintained as ≥ 50 × 10^9/L, and the time course of platelet counts. In both the L-PLUS 1 and L-PLUS 2 trials, responders were defined as patients who had a platelet count of >= 50 × 10^9/L with an increase of >=20 × 10^9/L from baseline. The efficacy results are summarized in Table 1 and 2.[2,11,e]

Table 1. L-PLUS 1 Trial: Proportion of Patients Not Requiring Platelet Transfusion Prior to Invasive Procedure and Proportion of Responders[2]

Endpoint	Proportion (n/N) Exact 95% confidence interval		Treatment difference (95% confidence interval) P value
	Lusutrombopag (N = 49)	Placebo (N = 48)	
Not requiring platelet transfusion prior to invasive procedure*	78% (38/49) (63, 88)	13% (6/48) (4.7, 25)	64 (49, 79) < 0.0001§
Responder‡ during study	76% (37/49) (61, 87)	6% (3/48) (1.3, 17)	68 (54, 82) < 0.0001§

* A platelet transfusion was required if the platelet count was less than 50 × 10^9/L.
§ Cochran-Mantel-Haenszel test with baseline platelet count as stratum; p value and confidence interval calculated using Wald method.
‡ Platelet count reached at least 50 × 10^9/L and increased at least 20 × 10^9/L from baseline.

Table 2. L-PLUS 2 Trial: Proportion of Patients Not Requiring Platelet Transfusion Prior to Invasive Procedure or Rescue Therapy for Bleeding Through 7 Days After Invasive Procedure and Proportion of Responders[2]

Endpoint	Proportion (n/N) Exact 95% confidence interval		Treatment difference (95% confidence interval) P value
	Lusutrombopag (N = 108)	Placebo (N = 107)	
Not requiring platelet transfusion prior to invasive procedure* or rescue therapy for bleeding from randomization through 7 days after invasive procedure	65% (70/108) (55, 74)	29% (31/107) (21, 39)	37 (25, 49) < 0.0001§
Responder‡ during study	65% (70/108) (55, 74)	13% (14/107) (7.3, 21)	52 (41, 62) < 0.0001§

* A platelet transfusion was required if the platelet count was less than 50 × 10^9/L.
§ Cochran-Mantel-Haenszel test with baseline platelet count as stratum; p value and confidence interval calculated using Wald method.
‡ Platelet count reached at least 50 × 10^9/L and increased at least 20 × 10^9/L from baseline.

[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 median (Q1, Q3) duration of platelet count increase to at least 50×10^9/L was 22 (17, 27) days in lusutrombopag-treated patients without platelet transfusion and 1.8 (0.0, 8.3) days in placebo-treated patients with platelet transfusion in L-PLUS 1 and 19 (13, 28) days in lusutrombopag-treated patients without platelet transfusion and 0.0 (0.0, 5.0) days in placebo-treated patients with platelet transfusion in L-PLUS 2.[2]

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for lusutrombopag. The safety of lusutrombopag was evaluated in 3 randomized, double-blind, placebo-controlled trials, L-PLUS 1, L-PLUS 2, and M0626, in which patients with chronic liver disease and thrombocytopenia were treated with lusutrombopag (N=171) or placebo (N=170) at a dose of 3 mg daily for up to 7 days prior to a scheduled procedure.[2]

The most common adverse reactions (those occurring in at least 3%) in the lusutrombopag-treated group compared to placebo across the pooled data from the three trials are headache (5% vs 4%). The incidence of serious adverse events was 5% (9 of 171 patients) in the lusutrombopag group and 7% (12 of 170 patients) in the placebo group. The most common serious adverse reaction reported with lusutrombopag was portal vein thrombosis. No adverse reactions resulted in discontinuation of lusutrombopag.[2]

Deaths

There were total of 5 deaths occurred in subjects with thrombocytopenia and CLD; all occurred in subjects treated with lusutrombopag, and none were considered study drug-related by the investigators. Two of the 5 subjects died as a direct complication of vessel perforation/injury during the invasive procedure; the maximum platelet count in these 2 subjects were 111,000/µL. In the remaining 3 of 5 subjects, onset of nonprocedural-related events with an outcome of death occurred 13 to 28 days after the last dose of lusutrombopag, suggesting no PK explanation for off-target toxicity or any other evidence of study drug involvement. One of the patients developed hematemesis while sleeping and severe upper gastrointestinal hemorrhage 28 days after last dose and died on the same day. The second patient had multi organ failure and sepsis 21 days after last dose and died on day 28 due to a cardiac arrest. The third patient was reported with decompensated liver cirrhosis 16 days after last dose, and on day 23, the patient suffered cardiopulmonary arrest and died. The maximum platelet count in these 3 subjects were 79,000/µL, and the events resulting in death are common complications in CLD subjects.[10,11]

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 THROMBOTIC/THROMBOEMBOLIC COMPLICATIONS

(b) (4) TPO receptor agonists have been associated with thrombotic and thromboembolic complications, (b) (4) with CLD. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. Portal vein thromboses were reported in 1% (2 of 171) of MULPLETA-treated patients and 1% (2 of 170)

of placebo-treated patients in 3 randomized, double-blind trials and were identified post-procedure in protocol-specified imaging.[2]

The risk associated with lusutrombopag include thrombotic and thromboembolic complications will be communicated in the Warnings and Precautions section of the label, as well as recommendations are to consider the potential increased thrombotic risk when administering lusutrombopag 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. The Warnings and Precautions section of the label also instructs prescribers that lusutrombopag should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. The Dosage and Administration section of the label instructs prescribers that lusutrombopag has been investigated only as a single 7-day once daily dosing regimen in clinical trials in patients with chronic liver disease. Patient Information as part of labeling in section 17 to inform patients regarding the potential risks of thrombotic and thromboembolic complications will also be included.[f,2]

6 Expected Postmarket Use

Lusutrombopag will be dispensed in an outpatient care setting, limited to when the patient is scheduled to undergo a procedure within 2 to 8 days after the last dose of lusutrombopag. Treatment is limited to 8-14 days prior to the scheduled procedure.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for lusutrombopag beyond routine pharmacovigilance and labeling that did not include a boxed warning. They did propose Patient Information as part of labeling to inform patients regarding the potential risks of thrombotic and thromboembolic complications.

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 lusutrombopag, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of lusutrombopag is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.[2,11,g]

[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.*

[g] Labeling negotiations were ongoing at the time of completion of this review. Indication statement is updated and significant changes to the proposed label made by FDA prior to negotiations.

DRISK and DHP have determined that if approved, a REMS is not necessary to ensure the benefits of lusutrombopag outweigh its risks. Lusutrombopag appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reactions observed with the use of lusutrombopag are thrombotic and thromboembolic complications. Labeling, including Warnings and Precautions will be used to communicate the safety issues and management of toxicities associated with lusutrombopag. Current treatment options for thrombocytopenia in CLD have been platelet transfusions, splenic artery embolization, splenectomy, and TIPS placement, which are associated with multiple limitations and complications. Since avatrombopag is the only other therapy approved for this indication, lusutrombopag would provide another treatment option for patients.

Lusutrombopag is a TPO receptor agonist like the currently approved drugs Nplate (romiplostim) and Promacta (eltrombopagare). Nplate is indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, splenectomy. Promacta is indicated for treatment of thrombocytopenia in patients with chronic ITP or hepatitis C infection or sever aplastic anemia. 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 added 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 outweighed its risks.[12,13] 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.[1]

Lusutrombopag is only being indicated for short-term use; compared to Nplate and Promacta, which are indicated for use on a chronic basis, the risk profile is different. Dosing of lusutrombopag should be started 8-14 days prior to the patient's planned procedure and administered for only 7 consecutive days. Thrombotic complications are the only common adverse events that are noted in the labels for Nplate, Promacta and lusutrombopag. 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 are not in the lusutrombopag label. Labeling discussions are ongoing for lusutrombopag, but at this time, the proposed labeling does not include a Boxed Warning. Similar to avatrombopag, the risk of thrombotic and thromboembolic complications will be communicated in the Warnings and Precautions section of the label, as well as recommended guidance to manage toxicities.[1,14] The Warnings and Precautions section of the label also instructs prescribers that lusutrombopag should not be administered to patients with CLD in an attempt to normalize platelet counts. Patient Information as part of labeling to inform patients regarding the potential risks of thrombotic and thromboembolic complications will also be included.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of lusutrombopag. The management of the risks associated with lusutrombopag treatment can be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

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

[14] Avatrombopag. Prescribing Information (last updated 05/2018).

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/s/

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05/23/2018

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