CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761136Orig1s000

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	BLA
Application Number	761136
PDUFA Goal Date	December 4, 2019
OSE RCM #	2019-989
Reviewer Name(s)	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	November 5, 2019
Subject	Evaluation of the Need for a REMS
Established Name	luspatercept
Trade Name	Reblozyl
Name of Applicant	Celgene Corporation
Therapeutic class	Erythroid maturation agent
Formulation	25 mg or 75 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	1 mg/kg once every 3 weeks by subcutaneous (SC) injection

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 Reblozyl (luspatercept) is necessary to ensure the benefits outweigh its risks. Celegene Corporation submitted a Biologic Licensing Application (BLA 761136) for luspatercept with the proposed indication for adult patients with beta thalassemia-associated anemia who require red blood cell (RBC) transfusions. The FDA-approved indication will be for the treatment of adult patients who require regular RBC transfusions. The risks associated with luspatercept include thromboembolism, hypertension, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

The efficacy of luspatercept was established in the applicant's registrational trial, BELIEVE. Although thromboembolism and hypertension are not unusual or rare in this patient population and may occur because of severe beta-thalassemia, or frequent blood transfusions, patients administered luspatercept may be at increased risk for these events. Embryo-fetal toxicity is based on non-clinical data of decreased fetal growth and organogenesis in pregnant rats and rabbits at the maximum human recommended dose. Recommendations provided in the labeling will be to counsel pregnant women on the potential risk of fetal harm. There were no risks or adverse reactions identified that require a box warning, and no deaths were identified in the clinical trial program for luspatercept.

DRISK believes that a REMS is not needed to ensure the benefits of luspatercept 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) Rebloyzl (luspatercept) is necessary to ensure the benefits outweigh its risks. Celgene Corporation submitted a BLA (761136) for luspatercept with the proposed indication for adult patients with beta thalassemia-associated anemia who require red blood cell (RBC) transfusions. 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

Luspatercept is an erythroid maturation agent consisting of a receptor fusion protein of a modified extracellular domain of human activin receptor type IIB.[1] Luspatercept exerts its mechanism of action by promoting erythroid maturation through differentiation of late-stage erythroid precursors. The Applicant submitted the following proposed indication for luspatercept:

- The treatment of adult patients with beta thalassemia-associated anemia who require RBC transfusions.

The FDA-approved indication will be approved as the treatment of adult patients who require regular RBC transfusions. Luspatercept is supplied as a 25 mg and 75 mg lyophilized powder in a single-dose vial

for reconstitution with a recommended starting dose of 1mg/kg once every 3 weeks by subcutaneous injection. Duration is expected until clinical improvement in hemoglobin levels are achieved.[a]

The intended setting where luspatercept is likely to be administered is in an inpatient setting or outpatient infusion center. The Applicant's proposed label did not include a Boxed Warning, and at the time of this writing, the draft label does not include a Boxed Warning for luspatercept.

Luspatercept is an NME[b] and has been granted orphan drug, breakthrough therapy and fast track designation. At the time of this writing, luspatercept has not been approved in any other jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for luspatercept for beta-thalassemia indication BLA 761136 relevant to this review:

- 06/14/2011: Initial IND Submission (IND 112562)
- 03/11/2013: Orphan Drug Designation granted
- 05/05/2015: Fast Track Designation granted for transfusion-dependent and non-transfusion-dependent Beta Thalassemia
- 09/17/2019: 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 luspatercept

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Beta-thalassemia is a congenital blood disorder characterized by genetic anomalies in the synthesis of the beta chains of hemoglobin, resulting in a range of moderate to severe anemia due to decreased RBC production.[2] Three forms of this condition have been identified: thalassemia major, thalassemia intermedia and thalassemia minor. Thalassemia major is likely to be identified within the first 2 years of life, resulting in severe anemia and regular blood transfusions, which may lead to growth retardation, hepatosplenomegaly and iron overload complications, as well as other metabolic conditions. Thalassemia intermedia is often present later in life with moderate anemia, these patients may not frequent blood transfusions. However, these patients may suffer from hypertrophy of erythroid marrow and other hematologic complications such as osteoporosis and erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine.[2] Patients with thalassemia intermedia are likely to experience gallstones and leg ulcers due to their increased risk of thrombosis as a result of hematologic complications described above. Thalassemia minor is clinically asymptomatic however some patients

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

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

may experience moderate anemia.[c] In clinical practice, beta-thalassemia is characterized by the frequency and severity of anemia based on the role of RBC transfusion therapy, and thus patients are usually categorized as having transfusion-dependent (TD) beta-thalassemia or non-transfusion dependent (NTD) beta-thalassemia.[3] Patients with TD beta-thalassemia require blood transfusion therapy for life, and the frequency of blood transfusions depend on the patient's hemoglobin levels while those with NTD beta-thalassemia require occasional transfusions if needed.
Approximately 90 million people globally are carriers of beta-thalassemia. Nearly 60,000 symptomatic patients are born annually, with higher incidence rates in the European Union at 1 in 10,000.[2] Beta-thalassemia is becoming increasingly common in large multiethnic cities in North America as represented in newborn screening programs based on data from the National Sickle Cell and Thalassemia Screening Program.[4,d]

3.2 Description of Current Treatment Options

There are currently no pharmacological therapies approved to treat beta-thalassemia. TD beta-thalassemia requires frequent RBC transfusion (clinically determined based on the severity of the patient's anemia) and iron chelation therapy. Inherent risks of frequent RBC transfusions may include hemolytic reactions such as auto-immune reactions as well as the potential risks of acquiring transfusion-related infectious disease transmission (this is rare).[2,3] Hypercoagulability leading to increased risks of thrombosis are also complications that could result from frequent RBC transfusion and iron chelation therapy. There remains an unmet medical need for patients requiring chronic management for this disease.

4 Benefit Assessment

The efficacy of luspatercept for adult patients with beta-thalassemia was evaluated in the BELIEVE trial (NCT 02604433).[1]

The BELIEVE trial was a multicenter, randomized, double-blind, placebo-controlled trial of 336 patients with beta thalassemia who required regular RBC transfusions with no transfusion-free period greater than 35 days during that period were randomized 2:1 to receive luspatercept (n=224) or placebo (n=112). Luspatercept was administered subcutaneously once every 3 weeks if a reduction transfusion requirement was observed or until unacceptable toxicity. Patients with alpha-thalassemia, major organ damage, recent deep vein thrombosis, stroke, or recent use of ESAs, immunosuppressants or hydroxyurea were excluded from the BELIEVE trial. The median age was 30 years old (range 18-66 years), 42% were male and 54% were white.

[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.*

The efficacy was based on the proportion of patients achieving RBC transfusion burden reduction by at least 33% from baseline, with a reduction of at least two units of RBCs for 12 consecutive weeks (from week 13 to week 24).

Forty-eight (21%) of patients receiving luspatercept met the primary endpoint at week 24 compared to 5 (4%) in the placebo with a p-value of <0.0001. Sustained reductions of RBC requirements through week 48 were seen in 44 (19%) of patients receiving luspatercept compared to 4 (3%) of patients in the placebo arm; also resulting in statistical significance.

The clinical team recommends approval under priority review status[5,e]

5 Risk Assessment & Safe-Use Conditions

The most common adverse reactions reported in at least 10% of patients receiving luspatercept included: headache (26%), bone pain (20%), arthralgia (19%), fatigue (14%), cough (14%), abdominal pain (14%), diarrhea (12%) and dizziness (11%).

The clinical team identified thrombosis/thromboembolism, hypertension, and embryo-fetal-toxicity as serious risks of concern.[1,f] These risks will be labeled in warnings and precautions. There are no risks or adverse reactions identified that require a boxed warning.

5.1 THROMBOSIS/THROMBOEMBOLISM

Thromboembolic events (TEEs) including deep vein thromboses, pulmonary embolus, portal vein thrombosis and ischemic strokes were reported in 3.6% (n=8/223) patients who received luspatercept in the BELIEVE trial. Patients with beta-thalassemia are at an increased risk of experiencing a TEE due to the nature of the disease, as well as patients with known risks factors for thromboembolism. Recommendations are to consider thromboprophylaxis in patients with beta thalassemia or those with known risks factors for experiencing a TEE, and appropriately monitor for signs and symptoms of thromboembolic events and treat accordingly.

5.2 HYPERTENSION

Across all clinical studies for luspatercept, hypertension was reported in 10% (n=61/571) luspatercept-treated patients. Grade 3-4 hypertension ranged from 1.8% to 8.6%. In normotensive patients with beta-thalassemia who received luspatercept, 13 (6.2%) developed systolic blood pressure >130 mm Hg and 33 (16%) developed diastolic blood pressure >80 mm Hg.

[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.*

[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.*

Recommendations are to monitor blood pressure prior to each administration and manage new onset hypertension or exacerbations of preexisting hypertension using anti-hypertensive agents.

5.3 EMBRYO-FETAL TOXICITY

Based on non-clinical reproduction studies, luspatercept may cause fetal harm when administered to a pregnant woman. Administration of luspatercept at concentrations at the maximum recommended human dose of 1.25mg/kg resulted in organogenesis and adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth and structural abnormalities in pregnant rats and rabbits. Recommendations are to advise pregnant women of the potential risk to a fetus.

There were no deaths reported in the clinical trial for luspatercept in adult patients with beta-thalassemia.

6 Expected Postmarket Use

Luspatercept is likely to be prescribed by internal medicine physicians and mid-level providers and administered in an inpatient or outpatient infusion setting. Healthcare practitioners who are likely to prescribe and/or administer luspatercept should be aware of the monitoring and management of the potential adverse effects of luspatercept.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of luspatercept (Reblozyl) based on the efficacy and safety information currently available.

Beta-thalassemia is a congenital blood disorder characterized by genetic anomalies in the synthesis of the beta chains of hemoglobin, resulting in a range of moderate to severe anemia due to decreased RBC production. Patients may present with a multitude of clinical problems because of severe anemia and those patients with TD beta-thalassemia require blood transfusion therapy for life, which can put the patient at risk for hemolytic and auto-immune reactions, as well as the risk of thrombosis. If approved, luspatercept would be the first pharmacological therapy approved to treat beta-thalassemia.

The efficacy of luspatercept was achieved in the applicant's registrational trial, BELIEVE, in which 21% of patients receiving luspatercept met the primary endpoint at week 24 compared to 4% in the placebo group. This result was statistically significant. Furthermore, statistically significant sustained reductions in RBC requirements were seen through the 48th week in 19% of patients receiving luspatercept compared to 3% of patients in the placebo arm.

Thromboembolism, hypertension, and embryo-fetal toxicity were identified as serious risks of concern and will be communicated in warnings and precautions of the label. Thromboembolism and hypertension are not unusual or rare in this patient population and may occur because of severe beta-thalassemia, or frequent blood transfusions. Embryo-fetal toxicity is based on non-clinical data of decreased fetal growth and organogenesis in pregnant rats and rabbits at the maximum human recommended dose. Recommendations provided in the labeling will be to counsel pregnant women on the potential risk of fetal harm. There were no risks or adverse reactions identified that require a box warning, and no deaths were identified in the clinical trial program for luspatercept.

Luspatercept is likely to be prescribed by healthcare practitioners who are aware of the monitoring and management of the potential adverse effects of luspatercept and administered in an inpatient or outpatient infusion setting.

Because of these reasons, DRISK and DHP agree that a REMS is not necessary to ensure that the benefits of luspatercept outweigh the risks of treatment. Efficacy was established in the applicant's registrational trial, and adverse events identified with luspatercept are not new or unusual seen in this patient population, especially those who require frequent RBC transfusions. There were no adverse events identified that will be labeled as a boxed warning.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for luspatercept for the treatment of adult patients who require regular RBC transfusions 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.

10 Appendices

10.1 REFERENCES

[1] Luspatercept (Reblozyl) draft US Prescribing Information, October 29, 2019

[2] Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis*. 2010 May 21;5

[3] Motta I, et al. Management of age-associated medical complications in patients with beta-thalassemia. Expert Rev Hematol. 2019 October 29.

[4] National Sickle Cell and Thalassemia Screening Program, 2018

[5] Midcycle Meeting clinical review slides, July 9, 2019

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAOMI S BOSTON
11/05/2019 03:24:27 PM

CYNTHIA L LACIVITA
11/05/2019 03:26:05 PM