CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761112Orig1s000

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	761112
PDUFA Goal Date	February 6, 2019
OSE RCM #	2018-1337
Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	November 23, 2018
Subject	Evaluation of the Need for a REMS
Established Name	Caplacizumab
Trade Name	Cablivi
Name of Applicant	Ablynx
Therapeutic class	von Willebrand factor-director antibody
Formulation	Intravenous (IV) Injection
Dosing Regimen	10 mg IV prior to a plasma exchange followed by a 10 mg subcutaneous injection after completion of plasma exchange on that day. 10 mg once daily following plasma exchange; then 10 mg once daily for 30 days after subsequent treatment during plasma exchange or plasma exchange period if immunological disease is not resolved.

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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 Cablivi (caplacizumab) is necessary to ensure the benefits outweigh its risks. Ablynx submitted a Biologic Licensing Application (BLA 761112) for the proposed indication in patients (b) (4) The FDA revised indication for caplacizumab will be in combination with plasma exchange for the treatment of adult patients with aTTP. The serious risk associated with caplacizumab is an increased risk of bleeding. The applicant did not submit a proposed REMS or risk management plan with this application.

In the clinical trial, there was a statistically significant reduction in TTP-related deaths, recurrence of TTP, and at least one treatment-emergent major thromboembolic event in the caplacizumab arm. Because the mechanism of action of caplacizumab interferes with a clotting factor, there may be an increased risk for bleeding. The mechanism of action of caplacizumab interferes with a clotting factor and there may be an increased risk for bleeding. Because of their scope of practice, hematologist and oncologist should be aware of how to manage this risk. DRISK's recommendation is that a REMS is not necessary to ensure the benefits of caplacizumab outweigh its risks.

1 Introduction

This review by DRISK evaluates whether a REMS caplacizumab is necessary to ensure the benefits outweigh its risks. Ablynx submitted a BLA (761112) for the proposed indication to be used in patients (b) (4) The FDA revised indication for caplacizumab will be in combination with plasma exchange for the treatment of adult patients with aTTP. The serious risk associated with caplacizumab is an increased risk of bleeding. The applicant did not submit a proposed REMS or risk management plan with this application. This application is being reviewed under the Division of Hematology Products (DHP).

2 Background

2.1 PRODUCT INFORMATION

Caplacizumab is a von Willebrand factor (vWF)-directed antibody construct that targets the A1 domain of vWF, and inhibits the interaction between vWF and platelets, preventing vWF-mediated platelet adhesion.[1,a] The intended setting in which the drug is likely to be administered is an inpatient setting or infusion center following a plasma exchange prior to or after a procedure. Caplacizumab is an NME[b] and was granted as an Orphan drug, as well as Fast Track and Priority Review. Caplacizumab is not marketed in any jurisdictions and does not belong to a class of drugs approved with a REMS.

2.2 REGULATORY HISTORY

[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.*

The following is a summary of the regulatory history for BLA 761112 relevant to this review:

- 04/14/2009: Orphan Drug granted
- 07/21/2017: Fast track designation granted
- 04/04/2018: Submission for BLA 761112 received
- 09/17/2018: 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 caplacizumab.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Acquired or immune-mediated thrombotic thrombocytopenic purpura (aTTP) is a rare and life threatening autoimmune disease that is characterized by severe blood dyscrasias such as thrombocytopenia, hemolytic anemia and organ ischemia, with an estimated annual incidence between 1 new case per 1 million people in the United States.[2] Mortality rates can be as high as 20% despite treatment, even with early intervention.[c,d]

3.2 Description of Current Treatment Options

There are currently no medications specifically approved for the treatment of aTTP. Standard treatment of aTTP includes daily therapeutic plasma exchange (TPE) with or without steroids in emergency until remission. A complete response to treatment is defined by a platelet count above 150 x 10^9/L for 2 consecutive days, together with normal or normalizing lactic acid dehydrogenase (LDH) and clinical recovery. A durable treatment response is defined as a response lasting at least 30 days after discontinuation of TPE.[2] Refractory disease is defined by no treatment response by day 30 and/or no durable treatment response by day 60. If patients do not respond to TPE after 4 days of standard treatment, rituximab may be added, or other therapies such as vincristine in severe cases.[2]

4 Benefit Assessment

Data from the Applicant's HERCULES trial was used to determine efficacy for the approval of caplacizumab.[3] HERCULES was a Phase 3, double-blind, randomized (1:1) placebo controlled multicenter trial that evaluated 145 patients randomized to receive either plasma exchange plus caplacizumab or plasma exchange plus placebo. Treatment with caplacizumab met the primary endpoint of a reduced number of TTP-related deaths, recurrence of TTP, or a major thromboembolic event as displayed in Table 1.

[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.*

Table 1: Patients with aTTP-related death, a recurrence of aTTP, or at least one treatment-emergent major thromboembolic event during caplacizumab treatment[1]

Number of patients with	Caplacizumab N=72 n (%)*	Placebo N=73 n (%)
TTP-related death	0	3 (4.1)
Recurrence of TTP (exacerbation)	3 (4.2)	28 (38.4)
At least one treatment-emergent major thromboembolic event	6 (8.5)	6 (8.2)
Total[a]	**9 (12.7)**	**36 (49.3)**

N = number of patients within the population of interest (by treatment group); n = number of patients with events; TTP = thrombotic thrombocytopenic purpura; ITT = intent to treat; * based on 71 patients who received at least one dose of study drug. [a] $p < 0.0001$

Based on these data, the medical officer recommends approval for caplacizumab, as patients who received study drug appeared to have a shorter time for platelet response. and there appeared to be a lower incidence in recurrent TTP.[3,e]

5 Risk Assessment & Safe-Use Conditions

The main serious risk of treatment with caplacizumab is an increased risk of bleeding. Currently, there is no proposal for a Boxed Warning; the Warnings and Precautions section of the label highlights the need to monitor for the risk of clinically significant bleeding. Recommendations are also to assess the benefit of using caplacizumab in patients with coagulopathies or taking oral anticoagulants.[1,3,f]

6 Expected Postmarket Use

The intended setting in which the drug is likely to be administered is an inpatient setting or infusion center following a plasma exchange prior to or after a procedure. Hematologist and oncologist are the likely prescribers, and it is expected that they would be aware of this risk and how to manage it in patients receiving caplacizumab.

7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a proposed REMS or risk management plan with this application.

[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.*

8 Discussion of Need for a REMS

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life threatening disease that can result in a 20% mortality rate, despite treatment with daily therapeutic plasma exchange (TPE) with or without steroids. There are currently no FDA approved medications with an indication to treat aTTP. Caplacizumab is a von Willebrand factor-directed antibody indicated to be used in combination with plasma exchange for the treatment of adult patients with aTTP. In the clinical trial, there was a statistically significant reduction in TTP-related deaths, recurrence of TTP. In the clinical trial, there was at least one treatment-emergent major thromboembolic event in the caplacizumab arm. Because the mechanism of action of caplacizumab interferes with a clotting factor, there may be an increased risk for bleeding. Because of their scope of practice, hematologist and oncologist should be aware of how to manage this risk. In the Warnings and Precautions section of the label, there are recommendations for monitoring patients for clinically significant bleeding and evaluating the benefit/risk of using caplacizumab in patients with underlying coagulopathies or who are taking oral anticoagulants. There is no Boxed Warning for caplacizumab recommended at this time. The clinical reviewer recommends approval of caplacizumab based on the efficacy and safety information currently available. DRISK and DHP agree that a REMS is not necessary for the approval of caplacizumab.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for caplacizumab 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 Appendices

10.1 References

[1] Caplacizumab draft FDA label, October 17, 2018

[2] Berangere S, et al. Thrombotic thrombocytopenic purpura. Blood, 2017; 129(21):2836-2846

[3] Midcycle slides BLA 761112 Caplacizumab, September 4, 2018

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/s/

NAOMI B REDD
11/26/2018

ELIZABETH E EVERHART
11/26/2018
I concur

CYNTHIA L LACIVITA
11/26/2018