CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761083Orig1s000

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	761083
PDUFA Goal Date	November 15, 2017
OSE RCM #	2017-1069, 2017-1070
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	October 10, 2017
Subject	Evaluation of Need for a REMS
Established Name	Emicizumab
Trade Name	Hemlibra
Name of Applicant	Genentech
Therapeutic Class	a bispecific antibody bridging factor IXa and factor X
Formulation(s)	
Dosing Regimen	3 mg/kg by subcutaneous injection once a week for the first 4 weeks, followed by 1.5 mg/kg once weekly

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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 Hemlibra (emicizumab) is necessary to ensure the benefits outweigh its risks. Genentech submitted a Biologic Licensing Application (BLA) 761083 for emicizumab with the proposed indication for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. The serious risks associated with emicizumab include thrombotic microangiopathy (TMA) and thromboembolism (TE). The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and DHP agree that a REMS is not needed to ensure the benefits of emicizumab outweigh its risks for the proposed indication. The TMA and TE events are serious, but the incidence is low (1.4%). Both events are associated with concomitant use of high-intensity of activated prothrombin complex Concentrate (aPCC) therapy (>100 unit/kg/day). There were no TMA/TE events reported in concomitant use of aPCC dose ≤ 100 unit/kg/day. If approved, the label will include a Boxed Warning to communicate the risk of TMA/TE.

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) Hemlibra (emicizumab) is necessary to ensure the benefits outweigh its risks. Genentech submitted a Biologic Licensing Application (BLA) 761083 for emicizumab with the proposed indication for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A with factor VIII inhibitors. This application is under review in the Division of Hematologic Products (DHP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Hemlibra (emicizumab), a new molecular entity,[a] is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure produced (b) (4) in Chinese hamster ovary (CHO) cells. Emicizumab bridges activated factor IX (FIXa) and factor X (FX) to restore the function of missing activated factor VIII (FVIIIa) that is needed for effective hemostasis. Emicizumab is proposed for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A with factor VIIII inhibitors. Emicizumab has no structural relationship or sequence homology to FVIIIa and does not induce or enhance the development of direct inhibitors to FVIII.

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

Emicizumab is proposed as [redacted] vials of 30 mg, 60 mg, 105 mg, and 150 mg to be given by subcutaneous injection. The recommended dose is 3 mg/kg once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly. Emicizumab is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

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

- January 10, 2014: Orphan drug designation granted for hemophilia A
- September 2, 2015: Breakthrough therapy designation granted.
- June 23, 2017: BLA 761083 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 there are no major safety concerns identified at this time that would require a REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Hemophilia A is a bleeding disorder characterized by congenital underproduction or dysfunction of Factor VIII (FVIII). Hemophilia A accounts for about 80% of all cases of hemophilia. In the United States, the prevalence of hemophilia A is 20.6 cases per 100,000 males.[b] In 2016, the number of people in the United States with hemophilia A was estimated to be about 20,000.[1]

About 50-60% of patients with hemophilia A have severe hemophilia (FVIII, 2% of normal), associated with the severest bleeding manifestations.[c] Approximately 25-30% of patients has moderate hemophilia (FVIII 2-5%) and manifest bleeding after minor trauma. Those with mild hemophilia A (FVIII 6-30%) compromise 15-20% of all people with hemophilia, these patients develop bleeding only after trauma or surgery. Acquired hemophilia A, caused by the development of an autoantibody to FVIII in a person with previously normal hemostasis, develops with a frequency of 1 case per 1 million population per year.

Approximately 20-30% of patients with hemophilia A develop inhibitors against FVIII after exposure to therapeutic FVIII concentrates. Inhibitors can develop very early during the course of FVIII therapy (within 50-150 days of treatment initiation). With half of all cases occurring before the age of 5 years, pediatric patients represent the population at highest risk of developing inhibitors.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[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.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Testing for inhibitors is indicated when bleeding is not controlled after infusion of adequate amounts of factor concentrate during a bleeding episode. The presence of inhibitors is indicated by failure of correction of clotting times with 1:1 mix with normal plasma. Inhibitor concentration is titrated using the Bethesda method as positive result ≥ 0.6 Bethesda units (BU), low-titer inhibitor ≤5 BU, and high-titer inhibitor>5 BU.

Management of bleeding or surgery in a patient with an inhibitor of FVIII is challenging because inhibitors bind to the infused factor and render it ineffective. Inhibitors are much more likely to occur in patients with hemophilia A and in those with severe disease. For a patients with a titer >5 BU with a high responding inhibitor and serious bleeding with a need for major surgery, a bypassing product is used.

A bypassing product is the first choice in a patient with hemophilia A or B who has a high-titer inhibitor and requires treatment for bleeding or surgery. These clotting factor products contain an activated form of a downstream clotting factor in the coagulation cascade. Activated factor VII (factor VIIa) can directly activate factor X, bypassing the need for factors VIII and IX. Available products include:

- Recombinant activated factor VII (rFVIIa, NovoSeven RT) carries a boxed warning: Thrombosis, serious arterial and venous thrombotic events may occur.
- Activated Prothrombin Complex Concentrate (aPCC, FEIBA) carries a boxed warning: Thromboembolic events: have been reported during postmarketing surveillance.

4 Benefit Assessment

The efficacy and safety of emicizumab were evaluated in two clinical studies (an adult and adolescent study (Study 1) and a pediatric study (Study 2). The medical officer concluded that Study 1 demonstrated statistically significant results.[d] And the interim analysis of Study 2 showed favorable efficacy. [2] In both Study 1 and Study 2, emicizumab was self-administered or administered by the caregiver subcutaneously in the home setting after administration of the first 5 doses in a controlled setting in the clinic and appropriate training of the patients or cargivers.

Study 1

Emicizumab prophylaxis was evaluated in a randomized, multicenter, open-label, phase 3 study in 109 adult and adolescent males (aged 12 to 75 years) with hemophilia A with FVIII inhibitors who previously received either episodic or prophylactic treatment with bypassing agents. Subjects received weekly emicizumab prophylaxis (Arms A, C, and D), 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter, or no prophylaxis (Arm B).

[d] 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.*

Subjects previously treated with episodic bypassing agents were randomized in a 2:1 ratio to receive emicizumab prophylaxis (Arm A) or no prophylaxis (Arm B).

Subjects previously treated with prophylactic bypassing agents were enrolled into Arm C.

Subjects previously treated with episodic bypassing agents who had participated in a non-interventional study (NIS) prior to enrollment, but were unable to enroll into Study 1 prior to the closure of Arms A and B, were enrolled into Arm D.

The primary endpoint was treated bleed (arm A, N=35; vs arm B, N=18): 22 patients (62.9%) in Arm A vs. 1 patient (5.6%) in arm B had no treated bleeds (p-value <0.0001). Annualized bleed rate (ABR) was 2.9% in arm A vs 23.3% in arm B, ABR ratio was 0.13 (p-value<0.0001). All secondary bleed endpoints, including all bleeds, treated joint bleeds, treated spontaneous bleeds, and treated target joint bleeds, met significance level.

Study 2

Emicizumab prophylaxis was evaluated in a single arm, multicenter, open-label clinical study in pediatric males (age < 12 years, or 12-17 years who weigh<40 kg) with hemophilia A with FVIII inhibitors. Subjects received emicizumab prophylaxis at 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter. The median observation time was 12 weeks (7-14 weeks).

At the time of the interim analysis, the clinical study enrolled a total of 20 male subjects. Nineteen subjects were < 12 years old and evaluable for efficacy. There were one patient (5.3%) had treated bleed.[e] Seven patients (36.8%) had all bleed.[f] One patient was treated for spontaneous bleed. There were no patient was treated with joint bleed and target joint bleed.

5 Risk Assessment

The safety data are based on pooled data from Study 1 and Studay2, as well as one phase I/II clinical trial, in which a total of 141 male subjects with hemophilia A received at least one dose of emicizumab as routine prophylaxis. The median duration of exposure across the studies was 20.9 weeks (3 -177 weeks). The most frequently reported adverse drug reactions (ADRs) observed in >=10% of subjects treated with at least one dose of emicizumab were injection site reactions and headache.

Three patients (2.1%) receiving emicizumab prophylaxis withdrew from treatment due to ADRs, which were thrombotic microangiopathy (TMA), skin necrosis and superficial thrombophlebitis, and injection site reaction.

No deaths were reported prior to the cutoff date in the clinical studies.

[e] Treated bleeds: bleeds treated with bypassing agents

[f] All bleeds: bleeds treated and not treated with bypassing agents

After the clinical cutoff date, a patient in Arm C in Study 1 receiving emicizumab prophylaxis developed a serious adverse event of TMA following concomitant bypassing agent treatment for a rectal hemorrhage, of which the latter was associated with a fatal outcome. The investigator assessed the patient death as related to the serious adverse event of rectal hemorrhage and unrelated to emicizumab, and the TMA as related to emicizumab and aPCC.

The most concerned ADRs are:

- Thrombotic microangiopathy (TMA) events: TMA events were reported in two patients (1.4%) from the safety data base. Each patient was reported to have received multiple doses of aPCC while receiving emicizumab prophylaxis prior to the development of TMA events (presenting with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury). One patient was discontinued emicizumab and no further aPCC was given. The patient underwent plasmapheresis and hemodialysis for which several doses of peri-procedural recombinant FVIIa were given. The other patient was diagnosed with TMA after having received 5 doses of aPCC over a span of 49 hours. Emicizumab was held, no further aPCC was given, and the patient was managed with supportive care.

  TMA resolved following discontinuation of aPCC in these two cases. Patients fully recovered from TMA within 3 weeks, with one patient resuming emicizumab therapy after resolution of TMA, without recurrence.

- Thromboembolic (TE) events: TE events were reported in two patients (1.4%) from the safety database. Each patient was reported to have received multiple doses of a PCC while receiving emicizumab prophylaxis prior to the development of TE events. One patient discontinued emicizumab and no further aPCC was given. The event resolved in18 days without anticoagulation, and emicizumab was restarted. The other patient was diagnosed with skin necrosis and superficial thrombophlebitis after having received 2 doses of aPCC. Emicizumab was discontinued and no further aPCC was given. The events of skin necrosis and superficial thrombophlebitis were resolved and the patient did not receive anticoagulation.[g]

If approved, the risks of TMA and TE will be communicated in labeling with a Boxed Warning.

Injection site reactions were reported in 18% of patients receiving emicizumab. The reactions included injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site pain, injection site pruritus, injection site rash, and injection site reaction. If approved, the label will contain a Warning and Precaution to convey the risk of injection site reaction.

Emicizumab affects assays for activated partial thromboplastin time (aPTT) and all assays based on aPTT, such as one-stage factor VIII activity. If approved, the label will contain a Warning and Precaution to

[g] 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.*

communicate that aPTT-based coagulation laboratory test results in patients treated with emicizumab should not be used to monitor emicizumab activity, determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titers.

6 Expected Post-market Use

Emicizumab, if approved, will be used at home by patients or caregivers after patients or caregivers are trained in the outpatient clinics or hemophilia treatment centers.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Clinical Reviewers recommend approval of emicizumab on the basis of the efficacy and safety information currently available. The Study 1 and Study 2 demonstrated favorable efficacy in adult and pediatric patients. Emicizumab is generally well-tolerated with infrequent serious adverse events.[3] If approved, the label will include a boxed warning to communicate the risks of TMA and TE.

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

In 2016, the number of people in the United States with hemophilia A was estimated to be about 20,000. About 20-30% of patients with hemophilia A develop inhibitors against FVIII after exposure to therapeutic FVIII concentrates. Inhibitors can develop very early during the course of FVIII therapy (within 50-150 days of treatment initiation). With half of all cases occurring before the age of 5 years, pediatric patients represent the population at highest risk of developing inhibitors.

For patients with a history of high-titer inhibitors (≥ 5 Bethesda units/ml) following a re-challenge with FVIII administration, the only hemostatic options currently available are prothrombotic coagulation factors that augment other parts of the coagulation cascade (commonly referred to as “bypassing agents”). These products include factor eight inhibitor bypassing activity (FEIBA): a plasma derived activated prothrombin complex concentrate (aPCC) and NovoSeven, recombinant activated human FVII (rFVIIa). Bypassing agents are not as effective at controlling or preventing bleeds in patients with inhibitors compared with FVIII concentrates in patients without inhibitors. In addition, treatment burden is high with the use of these agents that require frequent, high-volume, and/or extended intravenous infusion. There remains a high unmet medical need for prophylactic treatment options with low treatment burden patients with hemophilia A with inhibitors.

The medical reviewers concluded that emicizumab has favorable efficacy in adult and pediatric patients who have hemophilia A with inhibitors.

TMA and TE are potentially life-threatening adverse events that are associated with the administration of emicizumab. Both events are associated with concomitant use of high-intensity of aPCC therapy (>100 unit/kg/day). There were no TMA/TE events reported in concomitant use of aPCC dose ≤ 100 unit/kg/day. If approved, the risks of TMA and TE will be communicated in the label with a Boxed Warning.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, this reviewer has determined that a REMS is not necessary for emicizumab 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

10.1 References

[1] https://www.cdc.gov/ncbddd/hemophilia/data.html, accessed August 14, 2017

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9 George, JN & Nester CM. Syndromes of Thrombotic Microagiopathy, *N Engl J Med* 2014; 371:654-666

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/s/

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