CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	761369
PDUFA Goal Date	October 11, 2024
Nexus TTT #	2023-6699
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	October 8, 2024
Subject	Evaluation of Need for a REMS
Established Name	marstacimab
Trade Name	Hympavzi
Name of Applicant	Pfizer, Inc.
Therapeutic Class	Anti-tissue factor pathway inhibitor
Formulation(s)	subcutaneous injection (150 mg/mL single dose prefilled syringe, 150 mg/mL single dose prefilled pen)
Dosing Regimen	Day 1: 300 mg loading dose Day 8 and thereafter: 150 mg every week

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Hympavzi (marstacimab-hncq) is necessary to ensure the benefits outweigh its risks. Pfizer, Inc. (Applicant) submitted a Biologic Licensing Application (BLA 761369) for marstacimab with the proposed indication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors. The risks associated with marstacimab include thromboembolic events, hypersensitivity and embryofetal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of marstacimab outweigh its risks. In general, healthcare providers who treat hemophilia are familiar with the risks of thromboembolic events, hypersensitivity, and embryofetal toxicity and the importance of patient monitoring.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Hympavzi (marstacimab-hncq) is necessary to ensure the benefits outweigh its risks. Pfizer, Inc. (Applicant) submitted a Biologic Licensing Application (BLA 761369) for marstacimab with the proposed indication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors. This application is under review in the Division of Nonmalignant Hematology (DNH). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Marstacimab, a new molecular entity,[a] is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors. TFPI is the primary inhibitor of the extrinsic coagulation cascade.[1] It binds to and inhibits the factor Xa active site. The Applicant reports that marstacimab, a monoclonal antibody, mediates activation of the extrinsic pathway of coagulation via inhibition of TFPI, thus helping to restore coagulation balance and prevent bleeding in patients with hemophilia A or B. Marstacimab is proposed as a 150 mg/mL single-dose

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

prefilled syringe and 150 mg/mL single-dose prefilled pen for subcutaneous injection. The proposed dosing regimen is a loading dose of 300 mg administered by subcutaneous injection on Day 1, and maintenance dose starting one week later (Day 8) of 150 mg every week by subcutaneous injection. The dose may be adjusted to 300 mg subcutaneous injection weekly in patients weighing ≥50 kg when control of bleeding events is judged to be inadequate by the healthcare provider.[2] Marstacimab was granted orphan drug designation on May 18, 2016 and fast track designation on September 17, 2019. Marstacimab is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761369 relevant to this review:

- 05/18/2016: Marstacimab received Orphan Drug designation for routine prophylaxis to prevent or reduce the frequency of bleeding in Hemophilia A and Hemophilia B patients with or without inhibitors.
- 09/17/2019: Fast track designation granted for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A with inhibitors or hemophilia B with inhibitors.
- 10/11/2023: Marstacimab, BLA 761369, submission for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A and hemophilia B without factor VIII inhibitors, or factor IX inhibitors, respectively, received.
- 04/08/2024: 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, no major safety concerns had been identified to date.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hemophilia is the most common severe hereditary hemorrhagic disorder. It is characterized by prolonged and excessive bleeding after minor trauma or sometimes spontaneously.[3b] Hemophilia A and B result from coagulation factor protein deficiency or dysfunction that is typically due to a genetic defect or mutation. Hemophilia A results from a deficiency of clotting factor VIII and hemophilia B is due to a deficiency of factor IX. Both hemophilia A and B are inherited via an X-linked recessive pattern. The disorders predominantly affect males, although females who are heterozygous carriers can also be affected. The United States frequency rates of hemophilia A are estimated to be around 17 cases in 100,000 birth males, while rates for hemophilia B are approximately 3.3 cases per 100,000 birth males.[4]

[b] 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.*

It is estimated that as many as 33,000 males are living with hemophilia in the U.S.[5c] Severe hemophilia is a life-threatening disease characterized by significant morbidity resulting from recurrent spontaneous bleeds into the muscles, joints, gastrointestinal tract, or central nervous system leading to joints damage and poor quality of life. Due to the unpredictability of bleeding episodes and disease complications, individuals with hemophilia are at increased risk for mental health issues, such as depression and anxiety.[6]

3.2. Description of Current Treatment Options

There is no cure for hemophilia. The goal of hemophilia treatment is to prevent and treat bleeding, reduce complications and continue/resume normal activities of daily living.[7] The World Federation of Hemophilia developed treatment guidelines to serve as a clinical practice resource for hemophilia healthcare providers and patients. The guidelines recommend that people with hemophilia receive treatment in designated centers that have a multidisciplinary, comprehensive care model that ensures that people with hemophilia have access to a full range of clinical specialties and appropriate laboratory services.[8] There are approximately 140 hemophilia treatment centers in the United States.[9]

Current treatment options for patients with hemophilia A or B without inhibitors include, either an episodic intravenous (IV) infusion of the missing factor (FVIII or FIX) in response to symptoms of a bleed ("on-demand") or scheduled routine prophylactic factor VIII or IX administration to prevent bleeds from occurring. Prophylactic treatment with replacement factor VIII or IX has proven to reduce the frequency of bleeding events and complications such as joint destruction, however, it requires lifelong IV infusion every 1 to 2 weeks which can lead to treatment burden, incomplete adherence, and complications associated with indwelling catheters (i.e., infection, thrombosis).[10] Another concern with long term factor treatment is the development of alloantibodies that can block the activity of factor VIII or IX. Approximately 30% and 5% of patients with hemophilia A and B respectively, will develop neutralizing alloantibodies against infused factor VIII or IX.[11]

Another hemophilia treatment option is emicizumab which is a subcutaneously injected bispecific antibody that is FDA approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without inhibitor.[12] Emicizumab prescribing information includes a Boxed Warning due to reports of thrombotic microangiopathy and thromboembolism. At the time of this review, there is no approved non factor-based prophylactic treatment for patients with hemophilia B. The Applicant concluded that there is an unmet medical need for additional therapies that are non-factor based, effective for the hemophilia B population and offer convenient dosing.

[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.*

4. Benefit Assessment

The pivotal trial (study B7841005 [BASIS], NCT05145127) supporting this application consisted of a one-way, open label, multicenter, two-phase study. The study was conducted globally at 63 sites in 20 countries and consisted of 116 adult and pediatric male patients (aged 12 years and older and ≥35 kg) with severe[d] hemophilia A without FVIII inhibitors or severe hemophilia B without FIX inhibitors. Following screening, patients entered a 6-month observation phase and were enrolled in two separate cohorts based on the factor replacement treatment they were receiving prior to study entry: factor on demand (OD) or routine factor prophylaxis (PPX). Patients who completed the observation phase were to then receive 12 months of marstacimab. Of the 116 patients who received marstacimab, 33 patients were in the OD treatment cohort and 83 were in the prophylactic treatment with FVIII or FIX cohort during the observation phase. Patients received an initial 300 mg loading dose of marstacimab followed by maintenance doses of 150 mg once weekly for 12 months. Dose escalation to 300 mg of marstacimab once weekly was permitted after 6 months of treatment in patients weighing ≥50 kg and experiencing ≥2 breakthrough bleeds. Patients who completed the 12-month BASIS study were eligible to enroll in an open label extension study (study B7841007, NCT05145127).

The primary efficacy endpoint for study B7841005 is the annualized bleeding rate (ABR)[e] of treated bleeding events for the two cohorts. A comparison of ABR with marstacimab prophylaxis for each cohort is outlined below in Table 1 and 2.

[d] Severe hemophilia is defined as factor activity less than 1%.

[e] Annualized bleeding rate = number of bleeds requiring treatments/(days on treatment period/365.25).

Table 1. Comparison of Annualized Bleeding Rate with HYMPAVZI (marstacimab) Prophylaxis Versus on Demand Factor-Based Therapy in Patients ≥12 Years of Age without Factor VIII or Factor IX Inhibitors: Study B7841005[13]

Endpoints in the Order of Testing Hierarchy	On-Demand Factor-Based Therapy During 6-Month OP (N = 33)	HYMPAVZI Prophylaxis During 12-Month ATP (N = 33)
Treated Bleeds (Primary)		
ABR, model-based (95% CI)	38.00 (31.03, 46.54)	3.18 (2.09, 4.85)
Ratio vs. OD (95% CI)	0.084 (0.059, 0.119)	
p-value	<0.0001	
Spontaneous Bleeds, Treated		
ABR, model-based (95% CI)	30.93 (24.12, 39.67)	2.44 (1.61, 3.69)
Ratio vs. OD (95% CI)	0.079 (0.054, 0.114)	
p-value	<0.0001	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	32.86 (26.15, 41.29)	2.83 (1.81, 4.44)
Ratio vs. OD (95% CI)	0.086 (0.059, 0.125)	
p-value	<0.0001	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	47.76 (39.60, 57.60)	7.39 (5.08, 10.74)
Ratio vs. OD (95% CI)	0.155 (0.116, 0.207)	
p-value	<0.0001	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	23.18 (17.20, 31.24)	1.84 (1.06, 3.17)
Ratio vs. OD (95% CI)	0.079 (0.051, 0.124)	
p-value	<0.0001	

- p-value for the null hypothesis that the ratio = 0.5.
- The estimated mean, ratio, and confidence intervals (CIs) for the ABR come from a negative binomial regression model.
- Bleed definitions adapted based on ISTH criteria: Treated bleeds = bleeds treated with FVIII or FIX; Total bleeds = bleeds treated and not treated with FVIII or FIX
- ABR = Annualized Bleeding Rate; CI = Confidence Interval; OD = On-Demand; OP = Observational Phase; ATP = Active Treatment Phase

The medical officer concluded that marstacimab prophylaxis demonstrated superiority over on-demand factor-based therapy in incidences of treated bleeds, spontaneous bleeds, joint bleeds, total bleeds and target joint bleeds.

Table 2: Comparison of Annualized Bleeding Rate with HYMPAVZI (marstacimab) Prophylaxis Versus Previous Routine Factor-Based Prophylaxis in Patients ≥12 Years of Age without Factor VIII or Factor IX Inhibitors: Study B7841005[14]

Endpoints in the Order of Testing Hierarchy	Routine Factor-Based Prophylaxis During 6-Month OP (N = 83)	HYMPAVZI Prophylaxis During 12-Month ATP (N = 83)
Treated Bleeds (Primary)		
ABR, model-based (95% CI)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)
Difference vs. RP (95% CI)	−2.77 (−5.37, −0.16)	
Spontaneous Bleeds, Treated		
ABR, model-based (95% CI)	5.86 (3.54, 8.19)	3.78 (2.25, 5.31)
Difference vs. RP (95% CI)	−2.09 (−4.23, 0.06)	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	5.66 (3.33, 7.98)	4.13 (2.59, 5.67)
Difference vs. RP (95% CI)	−1.53 (−3.70, 0.64)	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	8.84 (5.97, 11.72)	5.97 (4.13, 7.81)
Difference vs. RP (95% CI)	−2.87 (−5.61, −0.12)	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	3.36 (1.59, 5.14)	2.51 (1.25, 3.76)
Difference vs. RP (95% CI)	−0.86 (−2.41, 0.70)	

- The protocol specified non-inferiority criterion (upper bound of the 95% CI for the difference) was 2.5 for treated bleeds, spontaneous bleeds, joint bleeds; 1.2 for target joint bleeds; 2.9 for total bleeds.
- The estimated mean, difference, and confidence intervals (CIs) for the ABR come from negative binomial regression model.
- Bleed definitions adapted based on ISTH criteria: Treated bleeds = bleeds treated with FVIII or FIX; Total bleeds = bleeds treated and not treated with FVIII or FIX
- ABR = Annualized Bleeding Rate; CI = Confidence Interval; OP = Observational Phase; ATP = Active Treatment Phase; RP = Routine Prophylaxis

The medical officer concluded that marstacimab prophylaxis demonstrated non-inferiority to routine prophylactic factor-based therapy as measured by ABR of treated bleeds as well as incidences of spontaneous bleeds, joint bleeds, target joint bleeds and total bleeds.

The Division of Non-malignant Hematology determined that substantial evidence of effectiveness of marstacimab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with: hemophilia A without factor VIII inhibitors or hemophilia B without factor IX inhibitor is established based on the results of the two independent cohorts of Study B7841005.[15]

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from 116 participants (33 from the OP-OD cohort, 83 from the OP-PPX cohort) who received at least one dose of marstacimab during the active treatment period of Study B7841005. No deaths were reported in any subject treated with marstacimab during the phase

3 trial. Eight serious adverse events (SAEs) were reported in 7 (6%) participants, all events occurred in the OP-PPX cohort and are outlined below in Table 3.

Table 3: Serious Adverse Events- Active Treatment Phase, Primary Safety Population Study B7841005

Serious Adverse Event	Marstacimab N=116 N(%)
Tympanic membrane perforation	1 (0.9)
Chest pain	1(0.9)
Peripheral swelling	1(0.9)
Tonsillitis	1(0.9)
Traumatic hemorrhage- injury	1(0.9)
Hemarthrosis	1(0.9)
Meningioma	1(0.9)
Hemorrhage	1(0.9)

The SAEs of meningioma, tonsillitis, and tympanic membrane perforation were assessed by the investigator to be unrelated to marstacimab. DNH agreed with this determination based on the mechanism of action of marstacimab. The SAEs of traumatic hemorrhage, hemorrhage, and hemarthrosis were considered by the investigator as unrelated to study drug. DNH concurred with this assessment and stated that the events were likely related to underlying disease.[16]

Adverse Events of Special Interest

5.1. Thromboembolic Events

Thromboembolic events are a potential risk with anti-hemophilic therapy. Marstacimab is a tissue factor pathway inhibitor antagonist and may increase the risk of thromboembolic complications due to its mechanism of action. No study participants with hemophilia reported thromboembolic events during treatment with marstacimab, but a healthy subject in the bioequivalence Phase 1 study B7841009, developed a thromboembolic event of pulmonary embolism and probable deep vein thrombosis (DVT) of the right posterior tibial vein 9 days after first receiving marstacimab and 29 days after vaccination with the second dose of the AstraZeneca (ChAdOx1-S [recombinant] vaccine) COVID-19 vaccine. The subject discontinued the study due to the DVT. The event resolved without sequelae and was considered related to marstacimab.[17] Draft Prescribing Information for marstacimab includes a Warning

and Precaution that thromboembolic events may occur and that treatment is to be interrupted if symptoms occur. The draft Patient Information sheet includes language about the possible risk of blood clots and the signs and symptoms of which patients should be aware. Additionally, DNH is recommending enhanced pharmacovigilance for thromboembolic events due to the small size of the safety database and limited duration of exposure for a drug that will be administered chronically.[18f]

5.2. Hypersensitivity

Hypersensitivity AEs are associated with biological agents and have the potential to be serious and life-threatening.[19] No severe or systemic cases of hypersensitivity or anaphylaxis occurred for participants in the Phase 3 study. In Study B7841005 three subjects reported events of stomatitis, rash and anaphylactic reaction. The anaphylaxis reaction was reported by an investigator for a subject who experienced urticaria and was treated with one tablet (a single dose) of loratadine and resolved without sequelae. The patient continued with his weekly dose of 150 mg marstacimab without further reaction. Draft labeling includes a Warning and Precaution that hypersensitivity reactions may occur and to discontinue marstacimab in the event of a severe allergic reaction. The draft Patient Information sheet informs patients about the possibility of severe allergic reaction and outlines the associated symptoms.

5.3. Embryofetal Toxicity

Animal studies to evaluate potential developmental toxicity with marstacimab treatment have not been conducted. There are no data from the use of marstacimab in pregnant women, but based on its mechanism of action it may cause fetal harm when administered during pregnancy. Draft labeling includes a Warning and Precaution that marstacimab may cause fetal harm and that females of reproductive potential should be advised to use effective contraception during treatment and for 2 months after the last dose; similar language is included in Section 8.1 Pregnancy. In Section 8.3 Females and Males of Reproductive Potential, healthcare providers are instructed to verify the pregnancy status of females of reproductive potential prior to initiating marstacimab treatment. In the draft Patient Information sheet it states that marstacimab may harm unborn babies. Additionally, there is text consistent with the embryofetal toxicity language in sections 8.1 and 8.3 of the draft Prescribing Information.

6. Expected Postmarket Use

Marstacimab is proposed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years and older with hemophilia A (without factor VIII inhibitors) or hemophilia B (without factor IX inhibitors). It is proposed as a single-dose prefilled syringe and single-dose prefilled pen for subcutaneous injection. Marstacimab will likely be prescribed and self-administered in the outpatient setting. Most hemophilia patients manage their disease through one of the 141 Hemophilia Treatment Centers which are federally funded facilities that provide comprehensive,

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

multidisciplinary care that can include hematologists with hemophilia expertise, nurse coordinators, physical and occupational therapists, counselors, social workers and other healthcare professionals.[20] The most likely prescribers of marstacimab will be hematologists who specialize in hemophilia treatment and have experience with managing the risks associated with anti-hemophilic therapies. In addition, patients with hemophilia are often knowledgeable about their disease, are able to identify treatment emergent adverse events such as thrombosis and hypersensitivity reactions and communicate concerns to their healthcare providers.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for marstacimab beyond routine pharmacovigilance and labeling. Draft labeling includes the Prescribing Information, Instructions for Use, and Patient Information sheet.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of marstacimab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors. Hemophilia is characterized by prolonged and excessive bleeding after minor trauma or spontaneously. Treatment often includes IV infusions on demand and/or prophylactically to replace missing clotting factors. Emicizumab, an FDA approved bispecific antibody is also used for prophylactic treatment of patients with hemophilia A with or without inhibitor. The DNH stated that there is an unmet medical need for additional treatment options.

Efficacy of marstacimab was demonstrated in a one-way, open label, multicenter, two-phase pivotal Phase 3 study by meeting the primary endpoint in a comparison of the annualized bleeding rate of treated bleeding events for the two cohorts. The adverse events of special interest associated with marstacimab were thromboembolic events, hypersensitivity and embryofetal toxicity; these risks are included in the Warnings and Precautions of the prescribing information for marstacimab. The risks were expected due to marstacimab's mechanism of action, anti-hemophilic properties, and use as a biological agent. One thromboembolic event was observed in a healthy subject during a Phase 1 trial but resolved without sequela. Thrombosis is also an identified risk for Emicizumab, the FDA approved bispecific antibody whose label includes a boxed warning for thrombotic microangiopathy and thromboembolism. Prescribers will likely be familiar with the risk and knowledgeable about managing it. Hypersensitivity is a common risk associated with biological agents. Prescribers and patients should be able to identify the signs and symptoms and respond appropriately as outlined in the prescribing information and Patient Information sheet. There were no animal reproduction studies in the clinical trial program, but the potential risk of embryofetal toxicity is referenced in multiple sections of the draft label and language is also included in the Patient Information sheet. The draft prescribing information recommends pregnancy testing before treatment initiation and the use of contraception during (and for 2 months after) treatment. The female population taking marstacimab would likely be limited as

hemophilia predominantly affects males. Women who are prescribed marstacimab will likely have their condition managed at a hemophilia treatment center or by a hemophilia specialist who can follow the recommendations outlined in the prescribing information.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits of marstacimab outweigh the risks. In general, healthcare providers who treat hemophilia are familiar with the risks of thromboembolic events, hypersensitivity and embryofetal toxicity and the importance of patient monitoring. Additionally, patients with hemophilia are often knowledgeable about their disease, able to identify treatment emergent adverse events such as thrombosis and hypersensitivity reactions and communicate concerns to their healthcare providers.

Should DNH have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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