Unit: Technical Assessment Unit

Public assessment report for biological products

Hympavzi

Administrative information:

Trade name of the medicinal product:	Hympavzi
INN (or common name) of the active substance(s):	Marstacimab
Manufacturer of the finished product	Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs-Sint-Amands 2870 - Belgium
Marketing Authorization holder	Pfizer Inc., 66 Hudson Boulevard East, New York, NY 10001-USA
Applied Indication(s):	- HYMPAVZI is a tissue factor pathway inhibitor (TFPI) antagonist indicated 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 (congenital factor VIII deficiency) without factor VIII inhibitors, or - hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.
Pharmaceutical form(s) and strength(s):	- Solution in prefilled pen - 150 mg/ml
Route of administration	Subcutaneous injection
Registration track	EMA, FDA approved

List of abbreviations

ABR annualised bleeding rate(s)
ADA anti-drug antibody
AE adverse event
aPCC Activated prothrombin complex concentrate
aPTT activated partial thromboplastin time
AUC Area under the concentration-time curve
AUCinf area under the concentration-time curve from 0 to infinity
AUC_{last} area under the concentration-time curve from 0 to time of last measurable concentration
AUCss area under the concentration-time curve at steady-state
AUC_{tau} AUC time curve during a dosing interval
C1q Complement factor 1q
CL clearance
C_{max} maximum (or peak) serum concentration
Cmax,ss maximum observed concentration at steady state
COVID-19 coronavirus disease 2019
dPT dilute prothrombin time
ECG electrocardiogram
FcγR Fragment crystallizable gamma receptor
FEIBA® activated prothrombin complex concentrate (aPCC)
FIX Factor IX
FVIIa/TF/FX factor VIIa/ tissue factor/ factor X complex
FVIII Factor VIII
FXa Factor Xa
IgG Immunoglobulin GI
IV Intravenous
K1 Kunitz Domain 1
K2 Kunitz Domain 2
mab monoclonal antibody
PD pharmacodynamics
PFP pre-filled pen
PFS pre-filled syringe
PK Pharmacokinetics

PTT Partial Thromboplastin Time
QW every week
RDT repeated dose toxicity
rFVIIa eptacog alpha
SC Subcutaneous
SPR Surface plasmon resonance
t½ terminal elimination half life
TFPI tissue factor pathway inhibitor
Tmax Time to peak drug concentration
TMDD target mediated drug disposition
Vc central volume of distribution

Table of contents

1. Introduction

The file evaluated according to EDA Reliance Model & the company submitted data which are the following:

1. Quality module-3 from the CTD file.
2. EMA Unredacted Assessment.

2. Quality aspects:

- **Manufacturer(s):**

- **Drug Substance**

- The Active substance is manufactured at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC 1 Burtt Road Andover, MA 01810 - United States of America Drug **product**

- The Finished product is manufactured at Pfizer Manufacturing Belgium NV Rijksweg 12 2870 Puurs-Sint-Amands - Belgium

- **Stability**

Drug substance:

- Approved shelf life for the active substance: 48 months

- Approved Storage Conditions of the active substance: Store at -25 °C to -15 °C

Drug product:

- Approved shelf life for the finished product: 36 months

- Approved Storage Conditions of the finished product:

- Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.
- If needed, HYMPAVZI may be stored at room temperature [up to 86°F (30°C)] in its original carton to protect from light for up to 7 days. Once stored at room temperature, do not return to the refrigerator and discard after 7 days.
- Do not freeze.
- Do not shake.

3. Non –clinical aspect:

Blood coagulation is achieved by a highly regulated cascade of plasma proteins, which ensures that bleeding can be rapidly stopped and that once bleeding is stopped, the cascade is shut down to prevent thrombosis. This regulation is achieved by 2 overlapping pathways, the *extrinsic* (initiation) and *intrinsic* (amplification) pathways, which converge in a final common pathway of coagulation.

Hemophilia A and B are bleeding disorders caused by a deficiency of coagulation Factor VIII (FVIII) or coagulation Factor IX (FIX), respectively, each of which is a key component of the *intrinsic* pathway.

They are hereditary, sex-linked, genetic diseases that are inherited in a recessive pattern. The genes encoding FVIII and FIX are on the long arm of the X chromosome and in hemophilia,

they are mutated. More than 1000 mutations in either the factor VIII or factor IX genes have been identified to cause clinical haemophilia. The genetic mutations cause a quantitative decrease in protein expression, a qualitative decrease in protein activity, or both. There is a high rate of spontaneous mutation (approximately one-third of cases) such that even in the absence of a family history, haemophilia should be suspected in a newborn with bleeding and a prolonged PTT.

Severity of hemophilia A or B is defined into 3 categories based on circulating FVIII or FIX activity levels in the plasma, each of which is characterized by different bleeding profiles. The most common haemophilia bleeds are prolonged spontaneous and/or traumatic bleeding within the musculoskeletal system and joints, as well as in the muscle and mucosal soft tissues. While less common, some types of bleeds, including intracranial and gastrointestinal bleeds, can be life-threatening. An individual's bleeding phenotype is the result of their genotype, joint health status and behaviour. Even among patients with severe hemophilia, there can be considerable heterogeneity in bleeding phenotypes.

Hympavzi is an IgG1 lambda human monoclonal antibody (mAb) that targets the Kunitz 2 (K2) domain of tissue factor pathway inhibitor (TFPI), an endogenous inhibitor of coagulation. Hympavzi binds to TFPI and inhibits its activity.

- **Pharmacology**:

The performed *in vitro* studies provided evidence for the binding of marstacimab to human, mouse, rat, rabbit and *Cynomolgus* monkey TFPI K1K2. Further SPR investigations endorsed binding to human TFPI K2 and non-binding to human TFPI K1. In a study that assesses Factor Xa activity restoration, a dose-dependent response of marstacimab was observed either in FXa or TF-FVIIa-FX Inhibition Reversal Assays. Marstacimab's inhibitory effect on TFPI in the extrinsic pathway leads to dose-dependent shortening of dPT clotting times in non-hemophilic human, rabbit and *Cynomolgus* monkey plasma, increased thrombin generation with increasing doses in non-hemophilic human plasma, while no effect on aPTT clotting time, which is focused on the intrinsic pathway of the coagulation cascade. Similar results were obtained in severe hemophilia A (with and without inhibitor) and haemophilia B plasma samples.

The combination of marstacimab and bypass agents (rFVIIa, aPCC or Byclot) in hemophilic plasmas (A and B) sometimes resulted in slight additivity in thrombin generation (peak thrombin level) but the concentration was within the range reported in studies for non-haemophilic normal plasmas.

In vivo, the pharmacodynamic effect of IV or SC marstacimab in *Cynomolgus* monkeys was demonstrated by shortening of dPT with a stable decrease in dPT clotting time from 24 to

240 hours. Additionally, the efficacy of intravenously administered marstacimab was shown in a model of disease, using acute tail clip injury and/or laser induced injury in hemophilia A and B mice. Combination studies in rats with marstacimab and bypassing agents (NovoSevenRT, FEIBA, or Byclot) did not raise major concerns regarding the combined effects of marstacimab and bypassing agents but with signs of enhanced efficacy for some combinations and doses.

It is of note that these combination studies are relevant primarily in the context of patients with inhibitors but marstacimab's indication in this application is only for haemophilia A and B patients without inhibitors.

Safety pharmacology was assessed within the toxicity study in *Cynomolgus* monkeys, where no test article-related changes were observed in neurological parameters, respiration rate, ECG parameters and hemodynamic endpoints.

- **Pharmacokinetics**:

  In *Cynomolgus* monkeys, the PK increased with dose and TMDD was observed at low doses. The mean t½ was between ~12 and 118 hours across doses in the nonclinical species. Also, in male rats, the potential additive effects of combined, repeated dosing of marstacimab together with NovoSeven RT, FEIBA, or ByClot were assessed. The mean systemic exposure (AUC) was similar in all dose groups when marstacimab was administered alone or in combination.

- **Toxicology**:

- The toxicologic profile of marstacimab was adequately examined with the submitted studies. However, the SC injection is the clinical route of administration and was more immunogenic than the IV route in the 3-month rat repeated-dose toxicity Study. It was expected that the long-term (6 month) SC administration study would adequately address the immunogenic potential of marstacimab in the rat, which wasn't the case. Nonetheless, as sufficient experience with subcutaneously administered marstacimab has already been gained in clinical trials, no concerns were raised regarding this aspect.
- Marstacimab was very well tolerated in rats and *Cynomolgus* monkeys. Importantly, all test-article related effects identified in the repeated dose toxicity studies pertained to the pharmacologic mode of action of marstacimab (enhancement of the extrinsic clotting pathway) or the presence of marstacimab itself.
- Based on the carcinogenicity risk assessment, a definitive link between TFPI inhibition with intermittent administration of marstacimab and risk of carcinogenesis has not been established. Moreover, marstacimab-related findings in the toxicity studies do not present

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a specific carcinogenicity concern. So, additional carcinogenicity studies are not warranted.

- No test-article related changes in male reproductive performance, spermatogenesis, embryonic survival and organ weights or macroscopic findings were observed in Study 00655204. The absence of other than male FEED studies in this submission is acceptable.
- No adverse local tolerance findings were observed in the 3-month rat RDT or the 8-day or 3-month monkey RDT studies at the IV or SC injection sites, respectively.
- Marstacimab's systemic exposure after IV dosing to rats and *Cynomolgus* monkeys increased dose-dependently in both species and drug accumulation was only observed in monkeys. No significant differences in PK parameters with regard to sex of the animals were observed in either species. Quantifiable levels of marstacimab were detected in rats through the recovery period in the 3- as well as the 6-month study, and in the 3-month RDT monkey study after 6 weeks of recovery.
- ADAs were only observed in the 3-month rat study after SC dosing and at the lowest IV dose (60 mg/kg/week), but not at higher IV doses, which may indicate that higher plasma levels of marstacimab may have interfered with ADA detection. However, ADAs did not appear to impact marstacimab exposure in ADA-positive rats, as exposure was similar to ADA-negative animals. No ADAs were detected in monkeys.
- Marstacimab didn't induce Tumor necrosis factor-alpha, Interleukin-6, nor Interferon-gamma release and didn't elicit C1q nor FcγR binding.

➢ **Overall conclusion**:

Marstacimab's mode of action, being a human monoclonal antibody directed against human TFPI, was demonstrated by in vitro and in vivo pharmacodynamic studies. Also, its combination with aPCC or Byclot was studied. No concerns were raised regarding safety pharmacology. The PK/TK profile of marstacimab was adequately examined using validated ligand-binding assays. The toxicologic profile of marstacimab was adequately studied. It was well tolerated in rats and Cynomolgus monkeys. All related effects identified pertained to the pharmacologic mode of action of the test-article or the presence of marstacimab itself.

4. Clinical aspect:

- The submitted dossier included seven clinical studies. Four phase I studies e; first in human phase I study **(B7841001)** to investigate the safety, tolerability, PK, and PD of SC and IV single ascending dose administration of marstacimab, an open-label phase Ib/II

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study **(B7841002)** to investigate the safety, tolerability, PK, PD, and efficacy of multiple SC doses of marstacimab, phase I open-label **(B7841009)** , crossover study to evaluate the bioequivalence of marstacimab **prefilled syringe and prefilled pen** following single-dose SC administration and finally phase I single-arm, open-label non-controlled multicentre study **(B7841010)** to evaluate the PK, PD, safety, and tolerability of a single subcutaneous dose of marstacimab in chinese adult participants with severe haemophilia.

- One Phase II study **(B7841003)** that as an open-label extension study of **(B7841002)** assessing the safety, tolerability, and efficacy of marstacimab as a prophylactic treatment regimen.
- Besides, two Phase III studies, **one pivotal phase III study (B7841005)** that was cross-over, open-label, multi-center study to demonstrate the efficacy and safety of PF-06741086 for routine prophylaxis in severe hemophilia A or moderately severe to severe hemophilia B using treatment on factor replacement or bypass therapy during the 6-month Observational Phase that is compared with a 12-month Active Treatment Phase. In addition to **(B7841007) study**; Phase III open-label **extension of Study (B7841005)** To determine the safety and tolerability of long-term treatment with marstacimab in severe hemophilia A or moderately severe to severe hemophilia B.

❖ **Clinical Pharmacology (PK & PD)**
  - **Study (B7841005) (Pivotal)**

PK Results:

- Marstacimab exposures (AUCss and Cmax, ss) were seen to increase with slightly greater than proportional increases over the 150 mg to 450 mg SC dose range.
- **Median steady-state marstacimab plasma concentrations** in adults receiving 150 mg weekly were approximately 10,000 - 11,000 ng/mL whereas median steady-state marstacimab plasma concentrations in adolescents were approximately 25,000 – 30,000 ng/mL (the weight-adjusted difference in CL and Vc between adolescents and adults was 3.1% and 25.9% respectively, indicating that weight explains most of the differences observed in CL between these two age groups and consequently most of the differences in PK between adults and adolescents).
- Marstacimab plasma concentrations increased following dose escalation to 300 mg SC QW and were higher than those seen with the 150 mg SC QW dose. Since accumulation of marstacimab and a potential risk for thrombosis could not be excluded, 6 participants had 3 PK data points (marstacimab concentration in plasma) after dose escalation, there was no sign of accumulation in these participants. For the remaining 8 participants, only one or two PK data points were available, the measured marstacimab concentrations were within the observed range of the overall study population.

PD Results:

- After weekly SC administration of 150 mg study drug (after a 300 mg loading dose), the PD biomarker of peak thrombin increased to physiological values and the measured downstream biomarkers for coagulation (PF 1+2, D-Dimer) **showed consistent response throughout the study**. This data supports the proposed dose regimen, which allows a dose escalation to 300 mg SC QW when control of bleeding events is judged to be inadequate by the healthcare professional. Dose escalation is permitted only for those subjects with a minimum bodyweight of 50 kg and only if the observed bleeding control is not deemed sufficient.

- **Study (B7841009):**

- The descriptive analysis of PK parameters of PFP and PFS for **18 participants** showed **comparable results** for both administration devices (PFP vs PFS: geometric mean AUC_{inf} [ng*hr/mL]: **2523000 vs. 2482000**; geometric mean AUC_{last} [ng*hr/mL]: **2018000 vs. 2015000**; geometric mean C_{max} [ng/mL]: 12550 vs. 12870; median T_{max} [hr]: 72.00 vs. 72.00). the study was terminated prematurely because of **the occurrence of a deep vein thrombosis and pulmonary embolism.** While the early termination of the study is not optimal, one could argue that this led to a more challenging scenario for meeting the acceptance criteria due to the lower sample size.

- PK from 11 participants who completed all 4 PK periods whose marstacimab administered via PFS versus PFP were demonstrated to **be bioequivalent with test/reference ratios of adjusted geometric means of marstacimab AUC_{last} and C_{max} values of 107.5% (95.2%, 121.4%) and 104.1% (93.7%, 115.6%), respectively. The confidence intervals are within the pre-specified acceptance range of 80% -125%.**

❖ **Clinical Efficacy**

- **Study (B7841005) and (B7841007):**

- Non-inferiority and statistical superiority regarding the ABR of treated bleeds were shown for weekly marstacimab prophylaxis over a prospectively conducted lead-in observational period on routine factor prophylaxis in the overall study population.

❖ **Clinical Safety**

The most frequently reported AEs irrespective of causality were COVID-19, headache, contusion and hypertension. The most frequent treatment related AEs were injection site reactions and prothrombin fragment 1.2 increased.

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- Hypertension was reported with more than twice frequency in the integrated dataset of Phase 2 studies 1002 and 1003 than in Phase 3 studies 1005/1007.

- Most of the elevations in blood pressure were episodic in nature as claimed by the applicant, and they occurred in patients who were normotensive or even low-normotensive at the baseline of Study 1005.
- One subject who discontinued from study B7841002 due to hypertension that resolved after stopping the study drug and the incidence of hypertension in 14% of subjects in phase 2 + extension studies and 7% of subjects in the phase 3 + extension studies, as well as the prolonged BP elevations occurring in normotensive patients during the Phase 3 studies, so it cannot ruled out convincingly that hypertension is related to marstacimab treatment, even if taking into account the comorbidity of hypertension with haemophilia.
- Hympavzi effectively reduced the frequencies of bleeding events in the overall patient population when compared to routine FVIII or FIX replacement prophylaxis during a run-in period of at least 6 months in the same subjects. Non-inferiority and statistical superiority over routine prophylaxis were shown in the combined analysis. Further, superiority over on-demand treatment was established.

- In conclusion the overall benefit/risk of Hympavzi injection in pre-filled pen (150mg/ml) is favorable in 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 a tissue factor pathway inhibitor (TFPI) antagonist.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/hympavzi-epar-public-assessment-report_en.pdf