Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research

Clinical Review Memorandum

To: File of STN 102865/5841

Mona Badawy, Regulatory Project Manager, RPMB IV/DRPM/OTAT

From: Chinwe Okoro, GMB3/DCEGM/OTP

Through: Elizabeth Hart, Branch Chief, GMB1/DCEGM/OTP

Subject: Final review of Pfizer's CBE Supplement to update the prescribing information for Thrombin, Topical (Bovine) U.S.P. [Thrombin-JMI®] including BOXED WARNING, RECENT MAJOR CHANGES, CONTENT, sections 5 WARNING AND PRECAUTION, 5.1 *Hypersensitivity Reactions*, 5.2 *Thrombosis*, 5.3 *Immunogenicity*, 8.1 *Pregnancy*, 8.2 *Lactation* 13.1 *Carcinogenesis, Mutagenesis, Impairment of Fertility*, Section 17 PATIENT COUNSELING INFORMATION

Cc: Gavin Imperato, Team Leader, GMB3/DCEGM/OTP
Kristine Khuc, PharmD, APLB/DCM/OCBQ

Executive Summary

Thrombin-JMI® is thrombin produced by activating bovine plasma-derived Prothrombin by thromboplastin isolated from bovine lung, in the presence of calcium chloride. *Thrombin-JMI*® is provided as a sterile powder in vials for reconstitution with its diluent (0.9% sodium chloride, United States Pharmacopeia) for topical use only. Currently, it is offered in two dosage strengths, 5,000 or 20,000 international units per vial. *Thrombin-JMI*® drug product vials can be packaged in either unit cartons or kits.

THROMBIN-JMI is indicated to aid hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

Pfizer submitted a Prior Approval Supplement (PAS) to the Biologics License Application for Thrombin, Topical (Bovine) U.S.P. [*Thrombin-JMI*®] on December 15th,

2022. The PAS was submitted with updated Prescribing Information in the Physician Labeling Rule (PLR) format.

The purpose of this PAS is to provide the following revisions to the existing United States Prescribing Information (USPI) for THROMBIN-JMI, based on FDA's request to comply with the Pregnancy and Lactation Labelling Rule (PLLR).

The following additional subsections has been proposed for revision to the USPI:

- BOXED WARNING
- RECENT MAJOR CHANGES CONTENT
- Section 5 Warnings and Precautions
- Section 8 Pregnancy Post-marketing Experience
- Section 8 Use in Specific Populations

In addition to the proposed changes from the Applicant, FDA requests modifications to various sections of the USPI to be consistent with current clinical practice and PLR formats. Administrative changes are requested for consistency and clarity.

Conclusion
Pfizer accepted FDA-recommended changes in the USPI, and the reviewer considers the revised PI to be acceptable. This reviewer recommends approval of the PAS, based on the final version of USPI received on June 13, 2023, under BLA 102865/5841.

Summary of Review
Pfizer initial revision of the label, led to the incorporation of USPI required language on pregnancy and lactation as shown below:

> **Risk Summary**
> Animal reproduction studies have not been conducted with THROMBIN-JMI. It is also not known whether THROMBIN-JMI can cause fetal harm when administered to a pregnant woman. THROMBIN-JMI should be given to a pregnant woman only if clearly needed.
>
> The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
>
> **Lactation**
> It is not known whether this drug is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for THROMBIN-JMI and any potential adverse effects on

the breastfed infant from THROMBIN-JMI or from the underlying maternal condition.

Reviewer Comment: This addition is satisfactory.

Upon further review following the satisfaction with the above revision. It was noted that the BOXED WARNING of the PI for *Thrombin-JMI*® did not include the references within the full prescribing information. The sponsor made the required revision, including the requisite references shown below.

WARNING: SEVERE BLEEDING AND THROMBOSIS COMPLICATIONS

See full prescribing information for complete boxed warning

- **THROMBIN-JMI can cause fatal severe bleeding or thrombosis. Thrombosis may result from the development of antibodies against bovine thrombin. Bleeding may result from the development of antibodies against factor V. These may cross-react with human factor V and lead to its deficiency. (5.2, 5.3)**
- **Do not re-expose patients to THROMBIN-JMI if there are known or suspected antibodies to bovine thrombin and/or factor V. (4, 5.3)**
- **Monitor patients for abnormal coagulation laboratory values, bleeding, or thrombosis. (5.3)**

Reviewer Comment: Satisfactory

Pfizer included the RECENT MAJOR CHANGES (below) to indicate the revisions made within the FPI.

----------RECENT MAJOR CHANGES ----------

Warnings and Precautions, Thrombosis (5.2)	M/2023
Warnings and Precautions, Immunogenicity (5.3)	M/2023

Reviewer Comment: Satisfactory

Pfizer revised sections 5.2 & 5.3 of the FPI to include additional information to support the statement within the BOXED WARNING, as well as provide clarity of the warnings.

5.2 Thrombosis

THROMBIN-JMI causes thrombosis if it enters the circulatory system due to its action in the clotting system. Apply topically. DO NOT INJECT.

5.3 Immunogenicity

Inhibitory antibodies may develop in patients and interfere with hemostasis. Do not re-expose patients to THROMBIN-JMI if there are known or suspected antibodies to bovine thrombin and/or factor V, due to the potential for these antibodies to interfere with hemostasis. Monitor patients for abnormal coagulation laboratory values, bleeding, or thrombosis.

Bleeding
Bleeding may result from the development of antibodies against factor V. These antibodies may cross-react with human factor V and lead to human factor V deficiency.

Thrombosis
Thrombosis may result from the development of antibodies against bovine thrombin.

Reviewer Comment: Satisfactory