Review Memorandum

Date:	**December 22, 2021**
To:	**The File**
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	Narayan Nair, MD (CBER/OBE)
Through:	**Peter Marks, MD, PhD (CBER/OD)**
Applicant:	**Janssen Biotech, Inc.**
Application Number:	**EUA 27205**
Product:	**Janssen COVID-19 Vaccine**
Subject:	**CBER Assessment of New Safety Information on Thrombosis with Thrombocytopenia Syndrome (TTS) following Administration of the Janssen COVID-19 Vaccine**

This review memorandum documents CBER's determination to provide new safety information regarding the serious risk of thrombosis with thrombocytopenia syndrome (TTS) following administration of the Janssen COVID-19 Vaccine in the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and in the Fact Sheet for Recipients and Caregivers for the Janssen COVID-19 Vaccine.

Summary

On December 6, 2021, during the meeting of the Advisory Committee on Immunization Practices COVID-19 Vaccines Safety Technical Work Group (VaST), the Centers for Disease Control and Prevention (CDC) presented an analysis of surveillance data on TTS following administration of the Janssen COVID-19 Vaccine based on reports received by the Vaccine Adverse Event Reporting System (VAERS) through August 31, 2021. Reports of TTS following the Janssen COVID-19 Vaccine were first identified in March 2021, eventually leading to a pause in the use of the vaccine that lasted from April 13 until April 23. Since the pause was lifted, FDA and CDC have continually monitored VAERS for additional cases of TTS and gathered additional information on cases reported prior to the pause. Updated information has been regularly shared with VaST. A previous analysis of VAERS data on TTS following administration of the Janssen COVID-19 Vaccine had included cases reported through July 8, 2021. The analysis of VAERS data based on TTS cases reported through August 31, 2021 provided new safety information on the serious risk of TTS following administration of the Janssen COVID-19 Vaccine. The data are summarized in the appended document entitled "Update on Thrombosis with Thrombocytopenia Syndrome (TTS)" (TTS VAERS Summary Document). The new analysis indicated that the TTS reporting rate following the Janssen COVID-19 Vaccine is higher than previously presented and that TTS deaths following the Janssen COVID-19 Vaccine are more common than known at the time of previous analyses. The new analyses also provided updated reporting rates of TTS, stratified by age group and sex, following administration of the Janssen COVID-19 Vaccine.

As noted in the TTS VAERS Summary Document, cases of TTS have been reported in males and females 18 years and older following the administration of the Janssen COVID-19 Vaccine. The overall reporting

rate of TTS was noted to be 3.83 cases per million Janssen COVID-19 doses administered, with the highest reporting rate in females ages 30-39 years (10.60 per million) followed by females ages 40-49 years (9.02 per million doses). Specifically, as of August 31, 2021, 54 confirmed TTS cases were reported following the administration of the Janssen COVID-19 Vaccine, and eight confirmed TTS deaths were reported following the vaccine. The rate of death due to TTS was noted to be 0.57 per million Janssen COVID-19 Vaccine doses.

Based on this analysis, CBER determined that the new safety information regarding TTS should be included in the Fact Sheets for the Janssen COVID-19 Vaccine. The Fact Sheet for Healthcare Providers also includes revisions to CBER's causality assessment to state that the currently available evidence supports a causal relationship between TTS and the Janssen COVID-19 Vaccine. The revisions to the Fact Sheets were made on December 14, 2021, and a summary of these revisions is provided below.

Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers)

Addition of a new Contraindication, as follows:

> "Do not administer the Janssen COVID-19 Vaccine to individuals with a history of thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine or any other adenovirus-vectored COVID-19 vaccine (e.g., AstraZeneca's COVID-19 vaccine which is not authorized or approved in the United States) *[see Warnings and Precautions (5.2)]*."

Revisions to the Warning and Precaution on TTS, to convey the following:

- TTS case definition used for the VAERS analysis- i.e., a thrombosis in an unusual location for a thrombus (i.e., cerebral vein, visceral artery or vein, extremity artery, central artery or vein) and new-onset thrombocytopenia (i.e., platelet count <150,000/μL) occurring any time after vaccination; or new-onset thrombocytopenia (i.e., platelet count <150,000/μL), thrombosis in an extremity vein or pulmonary artery in the absence of thrombosis at an unusual location, and a positive anti-PF4 antibody ELISA test or functional HIT (heparin-induced thrombocytopenia) platelet test occurring any time after vaccination.
- Updated information on occurrence of TTS based on VAERS data- specifically, that "Cases of TTS following administration of the Janssen COVID-19 Vaccine have been reported in males and females, in a wide age range of individuals 18 years and older, with the highest reporting rate (approximately 1 case per 100,000 doses administered) in females ages 30-49 years; overall, approximately 15% of TTS cases have been fatal."
- Revision to CBER's causality assessment to state "Currently available evidence supports a causal relationship between TTS and the Janssen COVID-19 Vaccine."

Fact Sheet for Recipients and Caregivers

Revisions to convey the following:

- Individuals who have "had a blood clot along with a low level of platelets (blood cells that help your body stop bleeding) following Janssen COVID-19 Vaccine or following AstraZeneca's COVID-19 vaccine (not authorized or approved in the United States)" should not receive the Janssen COVID-19 Vaccine.
- "Blood clots with low levels of platelets following the Janssen COVID-19 Vaccine have been reported in males and females, across a wide age range of individuals 18 years and older;

reporting has been highest in females ages 30 through 49 years (about 1 case for every 100,000 vaccine doses administered), and about 1 out of every 7 cases has been fatal.

Recommendation

Based on the analysis of VAERS data that included cases of TTS reported through August 31, 2021, CBER determined that the new safety information regarding TTS should be included in the Fact Sheets for the Janssen COVID-19 Vaccine. At the current time, CBER has determined that the known and potential benefits continue to outweigh the known and potential risks of the Janssen COVID-19 Vaccine. As per statute, the benefit-risk profile of this vaccine will continue to be reevaluated at regular intervals while it is being made available under EUA.

Appendix- TTS VAERS Summary Document

Update on Thrombosis with Thro