U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)

MEMORANDUM

Date:	March 13, 2023
To:	EUA 27205
From:	Jane Woo, M.D., M.P.H. Team Leader, Pharmacovigilance Branch 1 (PB1) Adamma Mba-Jonas, M.D., M.P.H. Branch Chief, PB1
Through:	Narayan Nair, M.D. Director, Division of Pharmacovigilance (DPV) Office of Biostatistics and Pharmacovigilance (OBPV), CBER
Applicant:	Janssen Biotech, Inc.
Application Number:	EUA 27205
Product:	Janssen COVID-19 Vaccine
Subject:	CBER Assessment of New Safety Information on Myocarditis and Pericarditis following Administration of the Janssen COVID-19 Vaccine, and Change in Conditions of Authorization to Require Reporting for Myocarditis and Pericarditis

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This review memorandum documents CBER's determination to provide new safety information regarding the serious risks of myocarditis and pericarditis 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. This memorandum also provides the FDA review for revising the Letter of Authorization for Janssen COVID-19 Vaccine to require, under the conditions of authorization, reporting for myocarditis and pericarditis by Janssen Biotech, Inc. and vaccination providers.

Background:

FDA/CBER continuously monitors the post authorization safety of COVID-19 vaccines through both active and passive surveillance as well as review of safety data submitted by the manufacturers. A CBER analysis of reports submitted to the Vaccine Adverse Event Reporting System (VAERS) revealed new safety information on the serious risks of myocarditis and pericarditis following administration of the Janssen COVID-19 Vaccine. In May 2021, myocarditis and pericarditis were identified as potential emerging safety concerns for the Janssen COVID-19 Vaccine, and preliminary data were presented to the VRBPAC on October 15, 2021.[1] On October 20, 2021, based on analyses completed by both the FDA and the sponsor, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to include myocarditis and pericarditis under section 6.2 Post Authorization Experience. FDA reviewed Janssen's analysis of postmarketing data on myocarditis and pericarditis in addition to conducting its own analysis of reports of myocarditis and pericarditis submitted to VAERS. Based on data through January 2022, the manufacturer reported elevated O/E for multiple age strata in both sexes (Appendix). FDA continues to closely monitor the accumulating postmarketing experience for this product and perform updated analyses (see below Summary of Issue).

Summary of Issue

Reports were categorized as cases of myocarditis and pericarditis based on criteria listed in the VAERS Standard Operating Procedures for COVID-19 [1]. Through 2/28/2023, 232 myocarditis and/or pericarditis cases following administration of the Janssen COVID-19 Vaccine were reported to VAERS, including 93 cases occurring within 7 days, and 131 occurring within 21 days after vaccination. With 18,982,882 doses administered as of 3/3/2023 [2], the overall reporting rate of myocarditis and pericarditis is approximately 12.2 per million Janssen COVID-19 Vaccine doses administered. Among total reported cases, 139 (59.9%) occurred among people 30 years of age or older; 82 were in females and 132 in males; 129 (55.6%) reports were classified as 'serious,' including 20 deaths. However, it is important to note that these report totals reflect cases that have been reported to VAERS, and not the number of cases that have been adjudicated by cardiologists to determine whether they meet the criteria for probable or confirmed myocarditis or pericarditis attributable to the Janssen COVID-19 Vaccine.

In addition to FDA's automated query of VAERS to identify reports of myocarditis and pericarditis and FDA's manual review of serious reports, we received information from the Centers for Disease Control and Prevention (CDC) on their adjudication of reports based on healthcare provider interview and/or medical record review. Through 2/16/2023, 93 cases (61 myocarditis and 32 pericarditis) have been adjudicated and confirmed to meet the CDC case definition for myocarditis and pericarditis [3]. Sixty-two (67%) cases were 30 years of age or older, 72 (77%) cases were serious reports including 7 deaths (of note, deaths were not attributed to vaccination). Almost all cases (92; 99%) occurred following dose 1. Sixty-four cases occurred in the 21-day risk window, and 38 cases occurred in the 7-day risk window.

CBER performed observed-to-expected analyses (O/E) using multiple risk windows, and multiple background rates [4], based on the above described VAERS and vaccine administration data [2]. The

[1]Nair, Narayan. Review of Post Authorization Safety Data for Janssen COVID-19 Vaccine (2021 VRBPAC) available at: https://www.fda.gov/media/153132/download

overall O/E reporting rate ratio, using CDC confirmed *(narrow analysis)* cases with (data lock point February 16, 2023) was 10.45 (95% CI 7.39, 14.34) within 7 days after vaccination. The overall O/E reporting rate ratio, using myocarditis and pericarditis reports from automated VAERS queries *(broad analysis)*, which included unconfirmed cases, (data lock point February 28, 2023) was 25.57 (95% CI 20.64, 31.32) within 7 days after vaccination. The elevated ratio of observed to expected myocarditis and pericarditis cases, using multiple risk windows (7-day and 21-day intervals following vaccination) and background rates, suggests increased risks of myocarditis and pericarditis following administration of the Janssen COVID-19 Vaccine. Specifically, additional analyses demonstrated that the O/E risk ratio during the 0 – 7-day interval, following vaccination, remained particularly elevated for multiple background rates, for both broad and narrow analyses. Some analyses for the 21-day risk window also showed elevated ratios, but the results were less consistent than for the 7-day risk window. In conclusion, post marketing data suggest increased risks of myocarditis and pericarditis, particularly within 0 – 7 days following administration of Janssen COVID-19 Vaccine. (Please see Appendix for FDA's analyses of O/E myocarditis and pericarditis cases after administration of the Janssen COVID-19 Vaccine.)

Based on CBER's analysis of VAERS data, including CBER review of serious cases and information on the cases confirmed by the CDC, and CBER's review of Janssen's analysis, CBER has now determined that the accumulating data suggest increased risks of myocarditis and pericarditis following administration of the Janssen COVID-19 Vaccine. Accordingly, CBER has determined that the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) should be revised to include myocarditis and pericarditis in Warnings and Precautions. CBER also determined that the Fact Sheet for Recipients and Caregivers should be revised to include information on the occurrence of myocarditis and pericarditis following administration of the Janssen COVID-19 Vaccine, instructions for potential vaccine recipients to inform vaccination providers of a history of myocarditis and pericarditis, and instructions for vaccine recipients to seek medical attention for symptoms of myocarditis and pericarditis. The revisions to the Fact Sheets are detailed below.

Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers)

Addition of a new Warning and Precaution for myocarditis and pericarditis, as follows:

> Myocarditis and Pericarditis
>
> "Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest increased risks of myocarditis and pericarditis, particularly within the period 0 through 7 days following vaccination.
>
> The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (*https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#myocarditis-pericarditis*)."

Fact Sheet for Recipients and Caregivers

> Revisions to convey the following:

- Instruction for individuals who have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart) to convey that information to the vaccination provider before receiving the Janssen COVID-19 Vaccine.
- "Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received the vaccine. In most of these people, symptoms began within 8 days following vaccination. The chance of having this occur is very low. You should seek medical attention right away if you have any of the following symptoms after receiving the vaccine:
    - Chest pain
    - Shortness of breath
    - Feelings of having a fast-beating, fluttering, or pounding heart."

Summary of changes to LOA Conditions of Authorization

The Janssen COVID-19 Vaccine Letter of Authorization (LOA), Conditions of Authorization, describe adverse event reporting requirements for the Sponsor (Condition F) and for vaccination providers (Condition T) for submission of reports to VAERS. Because some cases of myocarditis or pericarditis following vaccine administration may be conservatively managed and may not meet the definition of serious adverse events, Conditions F and T will be revised to require reporting for myocarditis and pericarditis by the Sponsor and vaccination providers. This will help ensure cases are reported by the Sponsor and vaccination providers. The Sponsor is conducting additional post-authorization observational studies to assess adverse events of special interest. The pre-specified list of adverse events of special interest (AESI) includes myocarditis and pericarditis (the LOA condition N is being updated to include myocarditis and pericarditis as a pre-specified AESI).

The revised Conditions F, N and T will be as follows (changes are in bold font):

Condition F. Janssen Biotech, Inc. will report to VAERS:

- Serious adverse events (irrespective of attribution to vaccination);
- **Cases of myocarditis;**
- **Cases of pericarditis;**
- Cases of Multisystem Inflammatory Syndrome in adults; and
- Cases of COVID-19 that result in hospitalization or death, that are reported to Janssen Biotech, Inc.

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Janssen Biotech, Inc.

Condition N. Janssen Biotech, Inc. will conduct post-authorization observational studies to evaluate the association between Janssen COVID-19 Vaccine and a pre-specified list of adverse events of special interest, including **myocarditis and pericarditis,** thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome, immune thrombocytopenia (ITP), along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Janssen COVID-19 Vaccine under this EUA in the general U.S. population (18 years of age and older), individuals who receive a booster dose, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Janssen Biotech, Inc. will provide

protocols and status update reports to the IND 22657 with agreed-upon study designs and milestone dates.

Condition T. Vaccination providers administering the Janssen COVID-19 Vaccine must report the following information associated with the administration of the Janssen COVID-19 Vaccine of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):

- Vaccine administration errors whether or not associated with an adverse event
- **Cases of myocarditis**
- **Cases of pericarditis**
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Janssen COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800- 822-7967. To the extent feasible, report to Janssen Biotech, Inc. by contacting 1-800-565-4008 or by providing a copy of the VAERS form to Janssen Biotech, Inc. (Fax: 215-293-9955, or by email JNJvaccineAE@its.jnj.com).

The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) for Janssen COVID-19 Vaccine is also being revised to reflect the revision to Condition T regarding VAERS reporting.

Summary of rationale for changes to LOA

Myocarditis and pericarditis are included as important identified risks in the Pharmacovigilance Plan (PVP) for Janssen COVID-19 Vaccine and in Section 6 Overall Safety Summary, sub section 6.2 Post Authorization Experience of the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers). With the current update to the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), myocarditis and pericarditis will also be included in Section 5 Warnings and Precautions, sub section 5.5 Myocarditis and Pericarditis.). To help ensure appropriate monitoring of such risks and protect public health, the Sponsor and vaccination providers will be required, under the conditions of authorization, to report all cases of myocarditis and pericarditis (regardless of seriousness) to VAERS. LOA condition N is also being updated to include myocarditis and pericarditis as a pre-specified AESIs for post-authorization studies.

Conclusions

- Based on the analysis of VAERS data as well as Janssen's own assessments, CBER determined that a Warning for myocarditis and pericarditis should be included in the Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and that information on myocarditis and pericarditis should be included in the Fact Sheet for Recipients and Caregivers. 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 for the authorized population and under the authorized conditions of use.

- For the reasons described in this memorandum, FDA will revise the Letter of Authorization for the Janssen COVID-19 Vaccine to require, under the conditions of authorization, reporting for myocarditis and pericarditis by the Sponsor and vaccination providers, and to include myocarditis and pericarditis as pre-specified AESIs for post-authorization studies.

References

[1] Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19. VAERS Team, Immunization Safety Office, Division of Healthcare Quality Promotion National Center for Emerging and Zoonotic Infectious Diseases Centers for Disease Control and Prevention. *https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf*

[2] CDC. COVID Data Tracker: CDC, 2021 *https://covid.cdc.gov/covid-data-tracker/#vaccinations*

[3] Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–982. https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm

[4] Gubernot D et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677.

APPENDIX

FDA analyses of observed-to-expected risk ratios for myocarditis and pericarditis cases after Janssen COVID-19 Vaccine

CBER performed an observed-to-expected analysis (O/E) of confirmed myocarditis and pericarditis cases reported to VAERS based on vaccine administration data[1] and published background rate[2] of myocarditis and pericarditis. There were 18, 979, 373 doses of Janssen COVID-19 Vaccine administered as of February 23, 2023. There is a wide range of background rates cited in literature, Gubernot (2021): *"The incidences of acute pericarditis and myopericarditis (cases of acute pericarditis that also demonstrate myocarditis) are unknown; however, the incidence of myocarditis is estimated to be **1–10 cases/100,000 persons annually**."*

[1] CDC. COVID Data Tracker: CDC, 2021

https://covid.cdc.gov/covid-data-tracker/#vaccinations

[2] Gubernot D et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677.

VAERS: Narrow Analysis (includes cases that have been adjudicated and confirmed to meet CDC case definitions; data lock point 2/16/23)

	≤ 7 days	≤ 21 days
All ages	38	64

VAERS: Observed-to-Expected Analysis – Narrow

Age (years)	Background Rate per 100,000 persons annually [a]	O/E ratio (95% CI)	
		7 days	21 days
All ages	1	10.45 (7.39, 14.34)	5.87 (4.52, 7.49)
	5	2.09 (1.48, 2.87)	1.17 (0.90, 1.50)
	10	1.04 (0.74, 1.43)	0.59 (0.45, 0.75)

[a] *Gubernot et al. Vaccine. 2021 Jun 23;39(28):3666-3677.* PMID 34088506.

VAERS: Broad Analysis (includes unadjudicated cases from automated VAERS query, data lock point 2/28/23)

	≤ 7 days	≤ 21 days
All ages	93	131

VAERS: Observed-to-Expected Analysis – Broad

Age (years)	Background Rate per 100,000 persons annually [a]	O/E ratio (95% CI)	
		7 days	21 days
All ages	1	25.57 (20.64, 31.32)	12.00 (10.04, 14.25)
	5	5.11 (4.13, 6.26)	2.40 (2.01, 2.85)
	10	2.56 (2.06, 3.13)	1.20 (1.004, 1.42)

[a] *Gubernot et al. Vaccine. 2021 Jun 23;39(28):3666-3677.* PMID 34088506.

Janssen: Observed-to-Expected Analysis (Safety summary 1/15/21-1/15/22; 22657.345)

Broad[a] analysis		O/E ratio[b] (95% CI)
Male	Age 18-29	3.595 (1.939, 6.090)
	Age 30-39	3.480 (1.545, 6.735)
	Age 40-49	4.580 (1.776, 9.647)
	Age 50-64	1.806 (0.523, 4.483)
	Age 65-74	1.413 (0.099, 6.094)
	Age ≥ 75	0.428 (0.000, 7.735)
Female	Age 18-29	23.069 (7.565, 53.539)
	Age 30-39	9.796 (3.750, 20.794)
	Age 40-49	6.971 (2.439, 15.601)
	Age 50-64	6.572 (2.682, 13.417)
	Age 65-74	3.648 (1.244, 8.285)
	Age ≥ 75	1.161 (0.010, 8.022)

[a]Broad: cases that occurred within the risk window (1-42 days), and cases for which the onset was 0 or not reported
[b]Background rates from *Baker et al. Am J Epidemiol. 2015 Apr 15;181(8):608-18.* PMID: 25769306

Case definition of myocarditis and pericarditis.

TABLE 1. Case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥1 new or worsening of the following clinical symptoms:*	Presence of ≥1 new or worsening of the following clinical symptoms:*
	• chest pain, pressure, or discomfort	• chest pain, pressure, or discomfort
	• dyspnea, shortness of breath, or pain with breathing	• dyspnea, shortness of breath, or pain with breathing
	• palpitations	• palpitations
	• syncope	• syncope
	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms:	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms:
	• irritability	• irritability
	• vomiting	• vomiting
	• poor feeding	• poor feeding
	• tachypnea	• tachypnea
	• lethargy	• lethargy
	AND	AND
	≥1 new finding of	≥1 new finding of
	• troponin level above upper limit of normal (any type of troponin)	• Histopathologic confirmation of myocarditis†
	• abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§	• cMRI findings consistent with myocarditis¶ in the presence of troponin level above upper limit of normal (any type of troponin)
	• abnormal cardiac function or wall motion abnormalities on echocardiogram	
	• cMRI findings consistent with myocarditis¶	
	AND	AND
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings

Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: • acute chest pain†† • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: • acute chest pain†† • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.