Our STN: BL 125742/641

NOTIFICATION
SAFETY LABELING CHANGE
April 17, 2025

BioNTech Manufacturing GmbH
Attention: Heather Hufnagel, MS
Pfizer Inc.
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Hufnagel:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for COVID-19 Vaccine, mRNA (COMIRNATY).

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and licensed biological product applications to make safety-related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Since COMIRNATY was approved on August 23, 2021, we have become aware of the following: (1) data from the Biologics Effectiveness and Safety System on the estimated incidence of myocarditis and/or pericarditis following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines, and (2) results from a postapproval study[1] in patients with COVID-19 vaccine-associated myocarditis showing persistence of abnormal cardiac magnetic resonance imaging findings that are a marker for myocardial injury at a median follow-up of approximately 5 months. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for mRNA COVID-19 vaccines. For COMIRNATY, we believe that the new safety information (NSI) should be included in the labeling as specified below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

RECENT MAJOR CHANGES

[1] Jain SS, Anderson SA, Steele JM, et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study. Lancet. 2024;76:1-13. https://doi.org/10.1016/j.eclinm.2024.102809

Warnings and Precautions, Myocarditis and Pericarditis (5.2) Month/Year

WARNINGS AND PRECAUTIONS

Replace “For COMIRNATY, the observed risk is highest in males 12 through 17 years of age” with the below NSI:

- Following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines, the highest estimated incidence of myocarditis and/or pericarditis was in males 16 through 25 years of age. (5.2)

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.2 Myocarditis and Pericarditis

Replace “For COMIRNATY, the observed risk is highest in males 12 through 17 years of age” with the following NSI:

Based on analyses of commercial health insurance claims data from inpatient and outpatient settings, the estimated incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines in individuals 6 months through 64 years of age was approximately 8 cases per million doses. The highest estimated incidence was in males 16 through 25 years of age (approximately 38 cases per million doses).

Add the following NSI:

Follow-up information on cardiovascular outcomes in hospitalized patients who had been diagnosed with COVID-19 vaccine-associated myocarditis is available from a longitudinal retrospective observational study. Most of these patients had received a two-dose primary series of an mRNA COVID-19 vaccine prior to their diagnosis. In this study, at a median follow-up of approximately 5 months post-vaccination, persistence of abnormal cardiac magnetic resonance imaging (CMR) findings that are a marker for myocardial injury was common. The clinical and prognostic significance of these CMR findings is not known (1) *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

Add the following NSI:

<u>Cardiovascular outcomes in patients diagnosed with mRNA COVID-19 vaccine-associated myocarditis</u>

In a longitudinal retrospective observational cohort study across 38 hospitals in the U.S., information on cardiovascular outcomes was collected on 333 patients 5 through 29 years of age who had been diagnosed with COVID-19 vaccine-associated myocarditis. Among these patients, 322 were confirmed to have received an mRNA COVID-19 vaccine encoding the S glycoprotein of the Original SARS-CoV-2. Of 331 patients, 278 had onset of symptoms following the second dose of a primary series, 33 following the first dose of a primary series, and 20 following a first booster dose (1).

Among 307 patients who had been diagnosed with COVID-19 vaccine-associated myocarditis for whom follow-up information was available, 89 reported cardiac symptoms at a median follow-up of 91 days (interquartile range 25 – 186 days) post-vaccination (1).

Initial gadolinium-enhanced cardiac magnetic resonance imaging (CMR) was performed on 216 patients, of whom 177 had late gadolinium enhancement (LGE), a marker of myocardial injury. Among 161 patients who had LGE on initial CMR and who had a follow-up gadolinium-enhanced CMR at a median follow-up of 159 days (interquartile range 78 – 253 days), 98 had persistence of LGE. Overall, the severity of LGE decreased during follow-up. The clinical and prognostic significance of these CMR findings is not known (1).

Limitations of this study include potential selection bias towards patients with more severe myocarditis who are more likely to be hospitalized and have CMR, variability in diagnostic testing, and variability in follow-up (1).

15 REFERENCES

Add the following reference:

1. Jain SS, Anderson SA, Steele JM, et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study. Lancet. 2024;76:1-13. https://doi.org/10.1016/j.eclinm.2024.102809

Patient Package Insert

Replace “Myocarditis and pericarditis following COMIRNATY have occurred most commonly in adolescent males 12 through 17 years of age” with the following NSI:

Based on available data, the estimated rate of myocarditis and/or pericarditis from 1 through 7 days after getting a dose of the 2023-2024 Formula of mRNA COVID-19 vaccines was approximately 8 per million doses in people 6 months through 64 years of age; the highest estimated rate was in males 16 through 25 years of age (approximately 38 cases of myocarditis and/or pericarditis per million doses).

Add the following NSI:

In a study, follow-up information was collected on people who developed myocarditis after receiving the original formula of a COVID-19 vaccine; most people had received an mRNA COVID-19 vaccine. Some people in the study reported having heart symptoms approximately 3 months after developing myocarditis. Some people in the study had heart MRIs (scans that show detailed images of the heart muscle) initially after developing myocarditis and again approximately 5 months later. The initial and follow-up heart MRIs commonly showed signs of injury to the heart muscle, with improvement over time in most people. It is not known if these heart MRI findings might predict long-term heart effects of myocarditis. Studies are underway to find out if there are long-term heart effects in people who have had myocarditis after receiving an mRNA COVID-19 vaccine.

In accordance with section 505(o)(4), within 30 calendar days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction or notify FDA that you do not believe a labeling change is warranted and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Under section 505(o)(4), if you fail to submit a response within 30 calendar days, you would be in violation of the FDCA that may deem your product to be misbranded under section 502(z) and may subject you to enforcement action, including civil monetary penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Please submit your safety labeling submission to STN 125742.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you have any questions, please contact the Regulatory Project Managers, Julianne Clifford, PhD by email at Julianne.Clifford@fda.hhs.gov, Meghan Maguire Thon, PhD by email at Meghan.MaguireThon@fda.hhs.gov and CAPT Michael Smith, PhD by email at Michael.Smith2@fda.hhs.gov.

Sincerely,

Richard Forshee, PhD
Director (Acting)
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research