Review Memorandum Addendum

Date:	**November 19, 2021**
To:	**The File**
From:	**David Cho, PhD (CBER/OD)**
Through:	**Peter Marks, MD, PhD (CBER/OD)**
Applicant name:	**ModernaTX, Inc.**
Application Number:	**EUA 27073**
Product:	**Moderna COVID-19 Vaccine**
Subject:	**Addendum to CBER's review memorandum dated November 18, 2021 entitled, "CBER Assessment of a booster dose of Moderna COVID-19 Vaccine (0.25 mL) administered following a primary COVID-19 immunization series in individuals 18 years of age and older"**

This addendum provides the Food and Drug Administration's (FDA, the Agency, or we) rationale for the recent revisions in the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to include updated information pertaining to the risk of myocarditis and pericarditis following the administration of the Moderna COVID-19 Vaccine.

Summary of Issue

The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was modified on November 19, 2021 to state:

> Some, but not all, observational analyses of postmarketing data suggest that there may be an increased risk of myocarditis and pericarditis in males under 40 years of age following the second dose of the Moderna COVID-19 Vaccine relative to other authorized or approved mRNA COVID-19 vaccines. Although postmarketing data following a booster dose of mRNA vaccines are limited, available evidence suggests a lower myocarditis risk following a booster dose relative to the risk following the primary series second dose.

As detailed below, the Agency is now aware of both public and non-public data that indicate that the rate of myocarditis and pericarditis in males under the age of 40 years of age is higher than

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

with the other authorized or approved mRNA vaccines.[1] These data were considered to be of relevance to providers when choosing which vaccine to administer to a specific individual.

Review

Myocarditis and pericarditis were identified as possible vaccine-related adverse events within a few months of the initial deployment of the mRNA COVID-19 vaccines. Reports from the Vaccine Adverse Event Reporting System (VAERS) suggested an elevated risk especially in males up to 40 years of age. Using myocarditis cases reported to VAERS with onset within 7 days after dose 2 of an mRNA vaccine, crude reporting rates (i.e., using confirmed and unconfirmed cases) per million second dose recipients were calculated using national COVID-19 vaccine administration data as of June 11, 2021. Myocarditis reporting rates were 40.6 cases per million second doses of mRNA COVID-19 vaccines administered to males aged 12−29 years and 2.4 per million second doses administered to males aged ≥30 years; reporting rates among females in these age groups were 4.2 and 1.0 per million second doses, respectively. The highest reporting rates were among males aged 12−17 years and those aged 18−24 years (62.8 and 50.5 reported myocarditis cases per million second doses of mRNA COVID-19 vaccine administered, respectively).[2]

Subsequently, evidence was communicated from other regulatory agencies, including agencies from Canada, France, Germany, Norway, and Japan that suggested that there was a higher rate of myocarditis/pericarditis observed in males under 40 years of age following the second dose of the Moderna COVID-19 Vaccine than with the Pfizer-BioNTech COVID-19 Vaccine. For example, Ontario, Canada reported a higher rate of myocarditis in individuals following the Moderna COVID-19 Vaccine than with the Pfizer-BioNTech COVID-19 Vaccine, particularly in males ages 18-24 years (https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-myocarditis-pericarditis-vaccines-epi.pdf?sc_lang=en).

FDA has conducted a post-market assessment for myocarditis and pericarditis cases using the Sentinel/BEST safety surveillance system. Preliminary findings from this ongoing assessment were presented at the October 14, 2021 meeting of the Vaccines and Related Biological Products Advisory Committee (https://www.fda.gov/media/153090/download). This study utilized four data partners to evaluate 12,677,102 Pfizer-BioNTech COVID-19 Vaccine doses and 8,557,588 Moderna COVID-19 Vaccine doses. No clear difference in the rate of myocarditis/pericarditis was identified at the time of the analysis.

[1] The other authorized or approved mRNA vaccines are Comirnaty (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine. The data summarized in this memo for the Pfizer-BioNTech COVID-19 Vaccine are also relevant to Comirnaty.

[2] 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. DOI: http://dx.doi.org/10.15585/mmwr.mm7027e2external icon

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

In contrast, the most recent data presented by the Center for Disease Control and Prevention (CDC) analyzed from the Vaccine Safety Datalink (VSD) indicates a higher rate of myocarditis with the Moderna COVID-19 Vaccine than the Pfizer-BioNTech COVID-19 Vaccine (Table 1).

Table 1. Summary of Myocarditis/Pericarditis Analyses Days 0-7 After Dose 2 Among 18-39 Year Olds: Excess Cases with Moderna COVID-19 Vaccine versus Pfizer-BioNTech COVID-19 Vaccine

Includes Pericarditis	**Sex**	**Adjusted Rate Ratio[1]**	**95% Confidence Interval**	**2-sided p value**	**Excess cases in risk period per million doses of Moderna vs Pfizer[2]**
Yes	Both	2.72	1.25-6.05	0.012	13.3
	Male	2.26	1.00-5.19	0.051	21.5
No	Both	2.28	1.00-5.22	0.049	9.7
	Male	2.14	0.93-4.98	0.074	19.1

[1] Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the Moderna COVID-19 Vaccine rate divided by the Pfizer-BioNTech COVID-19 Vaccine rate.

[2] Excess cases is an estimate of the Moderna COVID-19 Vaccine rate minus the Pfizer BioNTech COVID-19 Vaccine rate

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

Recommendation

Although the data are not yet dispositive that the rate of myocarditis and pericarditis observed in younger males receiving the Moderna COVID-19 Vaccine is higher than for other authorized or approved mRNA vaccines, most studies that the Agency is aware of suggest a difference in the rate of myocarditis and pericarditis between the Moderna COVID-19 Vaccine and other authorized or approved mRNA vaccines. To adequately counsel their patients regarding risks associated with various vaccine options, vaccination providers should be informed of this suggested difference. Therefore, the recent revisions in the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) include updated information pertaining to the risk of myocarditis and pericarditis following the administration of the Moderna COVID-19 Vaccine.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov