Office of Biostatistics and Epidemiology/Division of Epidemiology
Periodic Safety Report Review Checklist

Completed by Reviewer

Product Name	Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)
Manufacturer	Pfizer-BioNTech
STN #	19736.409
DCC Login ID #	Process Track ID: 693585
Submission Type	**PAER** ☐ **PSUR** ☐ **PBRER** ☐ **PADER** ☐
Submission Format	**ELECTRONIC** ☑ **PAPER** ☐
Reporting Period	**FROM** June 1, 2021 **TO** June 30, 2021
Date Received by FDA	July 15, 2021
Date Routed to Reviewer	July 15, 2021
Regulatory Information Specialist (RIS) - Name	Ramachandra Naik
Reviewer - Name	Deborah Thompson
Reviewer Signature (electronic signature)	Deborah L. Thompson -S Digitally signed by Deborah L Thompson -S DN c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2002552931 cn=Deborah L Thompson -S Date 2021 07 26 14 57 28 04 00'

COMMENTS

This is the 7th Summary of Monthly Safety Report (SMSR).

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1. Countries where the product is licensed or authorized for distribution:

   Not Reported ☐ US ☑ Worldwide ☑

2. Estimated number of doses distributed by reporting period/cumulative:

   Not Reported ☐ US (b) (4) period / (b) (4) cum

   Not Applicable ☐ Worldwide 239,476,397 period / 871,107,722 cum

3. Does this report describe any actions taken by the manufacturer or other regulatory agency for this product (e.g. labeling changes)? Yes ☑ No ☐

4. Have there been any new safety issues identified by the reviewer in this PSUR? Yes ☑ No ☐

If YES, please provide pertinent information below AND notify/discuss safety issues with the Team Lead and/or Branch Chief.

During this reporting period, local labels were updated to address the findings of myocarditis and pericarditis following vaccination with BNT162b2, including the U.S. Fact Sheet; a warning is also being added to the company Core Data Sheet. EMA and other global health author ties have also requested distribution of a Direct Health Care Professional (DHCP) letter to address these findings. As requested by FDA, in this SMSR the company used three background rates for myocarditis, a low (i.e., 1.92 per 100,000 PY), mid (4.40 per 100,000 PY), and high (9.95 per 100,000 PY) rate and also stratified the O/E analysis by sex, age groups, dose number, and EU or U.S. The overall O/E analysis using the low, mid, and high background rate revealed a cumulative O/E <1. However, the interval (June 1-30, 2021) O/E using a low background rate (and 21-day risk window) was 2.052 (95% CI 1.822-2.303) and the O/E using a mid background rate (and 21-day risk window) was 0.895 (95% CI 0.795-1.005). For the U.S., the cumulative O/E analysis using a 14-day risk window, revealed elevated O/E >1 with 95% CI >1 (for low, mid, and/or high background rates) for males age < 17 yrs, males age 18-24 yrs, females age 18-24 yrs, and overall post-dose #2.

The safety signal of dizziness was evaluated and determined not to be a risk.

Thrombocytopenia Thrombosis Syndrome (TTS) is an ongoing topic of review; the sponsor reports that the data do not support a causal association with the vaccine, but the topic will continue to be closely monitored. The company reports 97 reports of TTS meeting Brighton Collaboration (BC) Level 1, five reported a positive test for PF4-antibodies and an additional 11 (with no PF4 antibody resu ts) reported d-dimers >4000. The 16 reports meeting BC Level 1 with PF4-antibodies positive or d-dimer >4000 were all foreign reports; these patients had a median age of 73 yrs (range 31-90 yrs), 10 were male and 6 were female, onset post-vaccination ranged from the day of vaccination to 74 days later (9 cases occurred within 1 week post-vaccination).

Immune thrombocytopenia (ITP) is under re-evaluation due to receipt of post-authorization reports, request from EMA to review in PSUR #1, and FDA OBE finding of elevated O/E in CMS database; ITP was reviewed previously in January 2021 and will be reviewed again in PSUR #1 (new signal). The company's current O/E analysis for ITP reveals an O/E <1.

Menstrual disorders are under review for inclusion in PSUR #1 as requested by EMA.

The age stratification O/E analysis had higher ratios for at least one of the risk periods or risk windows for at least one of the age groups for transverse myel tis (TM), disseminated intravascular coagulation, and multisystem inflammatory syndrome (MIS). TM previously had an upper limit of the 95% CI of O/E ratio >1 and was reviewed in detail in the March SMSR; at that time, the signal was determined not to be validated. The background rate for TM was changed in the April 2021 SMSR to a lower background rate from the ACCESS database w th subsequent higher O/E ratios than in previous SMSRs. DIC had an elevated O/E ratio in the interval period for the 14-day and 21-day risk windows for the < 17 years age group; one case of DIC caused the O/E ratio to exceed 1, which was a neonate with in utero exposure. MIS had an elevated O/E ratio in the interval period for 18-24 yr, 25-49 yr, and 50-59 yr age groups; MIS also had a low number of cases w thin each age groups (i.e., < 5 cases), which could contribute to variability in the analysis. TM, DIC, and MIS will be monitored; TM and MIS will be further reviewed and discussed in the next SMSR.

The company also reported an O/E ratio of 3.982 (95% CI 3.858-4.108) for anaphylaxis (previously identified risk) compared to the background rate for anaphylaxis cases observed in the U.S; the O/E ratio has continued to decline from previous SMSRs.

Conclusions:

☑ The contents of this PSUR/PAER do not indicate a need for further regulatory action.

☐ Please see the following comments and recommendations:

Reference Documents (X:\DE\MEDICAL OFFICER\Guidance Documents):

1. E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs 1996
2. Addendum to E2C Safety Data Management: Periodic Safety Update Reports for Marketed Drugs 2004