Updated summary of risk management plan for Comirnaty (COVID-19 mRNA vaccine)

This document is a summary of the updated risk management plan (RMP) for Comirnaty, the Pfizer-BioNTech COVID-19 mRNA vaccine. The RMP is created by the vaccine manufacturer and is submitted to medicine regulators as part of the vaccine approval and safety monitoring processes. The RMP details important risks of Comirnaty, how these risks can be minimised, and how more information will be obtained about Comirnaty's risks and uncertainties (missing information).

Over time, the RMP is updated as more information becomes available, including any new risks or changes to current ones. This RMP update was made in conjunction with the extension of the indication to children 5 to 11 years of age.

The Comirnaty data sheet, consumer medicine information and the package leaflet give essential information for healthcare professionals and patients on how to use the vaccine.

Search for a data sheet or consumer medicine information

RMP definitions

Important risks

Important risks need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks are classified as identified or potential.

- Identified risks are concerns for which there is sufficient proof of a link with the use of the medicine.
- Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Activities to minimise or further characterise identified risks

Measures to minimise the identified risks for medicinal products may include:

- specific information for healthcare professionals and patients, such as warnings, precautions and advice on correct use, in the data sheet, consumer medicine information and package leaflet
- important advice on the medicine’s packaging
- the authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- the medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously by the company and regularly analysed, so that immediate action can be taken by the company as necessary. These measures constitute *routine pharmacovigilance activities*.

Other non-routine Measures to further characterise the risks include safety and efficacy studies. The studies may be in particular risk groups or for particular safety concerns. They may also be a condition of the medicine's approval. These measures constitute *additional pharmacovigilance activities*.

Comirnaty RMP

The medicine and what it is used for

Comirnaty is a vaccine for active immunisation to prevent COVID-19 caused by SARSCoV-2 virus, in individuals 5 years of age and older (see the data sheets for the full indication). The vaccine contains nucleoside-modified messenger RNA encapsulated in lipid nanoparticles as the active substance and it is given intramuscularly.

There are 2 different strengths of Comirnaty:

- 30 mcg/dose for immunisation of individuals aged 12 years and older
- 10 mcg/dose for immunisation of individuals aged 5 to 11 years.

Important risks, missing information and additional pharmacovigilance activities

The tables below summarise the risks for Comirnaty, as described in the updated RMP.

- Table 1 is a list of the important risks (identified and potential) and missing information.
- Tables 2–10 provide the evidence for linking the risk to the medicine, risk factors and risk groups, risk minimisation measures and a list of additional pharmacovigilance activities.
- Table 11 summarises the additional pharmacovigilance activities.

Table 1: List of important risks and missing information

Important identified risks	Anaphylaxis Myocarditis and pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Table 2: Important identified risk: Anaphylaxis

Evidence for linking the risk to the medicine	Events of anaphylaxis have been reported.
Risk factors and risk groups	Known allergy to the vaccine or its ingredients.
Risk minimisation measures	Routine: Data sheet sections 4.4. and 4.8. Additional: None.
Additional pharmacovigilance activities*	C4591001 C4591009 C4591010 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU)

* See Table 11 for a summary of the studies.

Table 3: Important identified risk: Myocarditis and pericarditis

Evidence for linking the risk to the medicine	Events of myocarditis and pericarditis have been reported.
Risk factors and risk groups	Most frequently reported in adolescent and young adult male patients following the second dose of vaccine; however, reports have been received for males and females of broader age range and following the first vaccination also.
Risk minimisation measures	Routine: Data sheet sections 4.4. and 4.8. Additional: Letter to healthcare professionals (DHCP) and communication plan.

Additional pharmacovigilance activities*	C4591009 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 sub-study) C4591036 (former Pediatric Heart Network study)

* See Table 11 for a summary of the studies.

Table 4: Important potential risk: Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

Evidence for linking the risk to the medicine	VAED is considered a potential risk because it has not been seen in human studies with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus. VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease.
Risk factors and risk groups	It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time.
Risk minimisation measures	Routine: None Additional: None
Additional pharmacovigilance activities[a]	C4591001 C4591009[b] C4591011[b] C4591012[b] C4591021 (former ACCESS/VAC4EU)[b]

a. See Table 11 for a summary of the studies.

b. The study addresses safety events of interest, including vaccine-associated enhanced disease.

Table 5: Missing information: Use in pregnancy and while breast feeding

Risk minimisation measures	Data sheet section 4.6
Additional pharmacovigilance activities[a]	C4591009[b] C4591010[b] C4591011[b] C4591015 C4591021 (former ACCESS/VAC4EU)[b]

a. See Table 11 for a summary of the studies.

b. Studies C4591009, C4591010, C4591011 and C4591021 address only 'Use in pregnancy'.

Table 6: Missing information: Use in immunocompromised patients

Risk minimisation measures	Data sheet sections 4.4 and 5.1.
Additional pharmacovigilance activities[a]	BNT162-01 cohort 13 C4591010[b] C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and Immunogenicity in high-risk adults)

a. See Table 11 for a summary of the studies.

b. The study addresses safety events of interest.

Table 7: Missing information: Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	Data sheet section 5.1.
Additional pharmacovigilance activities*	C4591001 subset C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults)

* See Table 11 for a summary of the studies.

Table 8: Missing information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	None
Additional pharmacovigilance activities*	C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults)

* See Table 11 for a summary of the studies.

Table 9: Missing information: Interaction with other vaccines

Risk minimisation measures	Data sheet section 4.5
Additional pharmacovigilance activities*	C4591030 (Co-administration study with seasonal influenza vaccine)

* See Table 11 for a summary of the studies.

Table 10: Missing Information: Long term safety data

Risk minimisation measures	None
Additional pharmacovigilance activities*	C4591001 C4591010 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 substudy) C4591036 (former PHN)

* See Table 11 for a summary of the studies.

Studies

Table 11: Summaries of the Comirnaty studies listed in Tables 2–10

Study	Purpose of the study
C4591001	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An unfavourable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.
C4591009	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System (FDA's national electronic system).
C4591011	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.
C4591012	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use (individuals in the US Veteran's Affairs Health System) of COVID-19 mRNA vaccine.
C4591010	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.
C4591015	To assess safety and immunogenicity in pregnant women. In addition, exploratory objectives include:

	(a) To describe the immune response in infants born to breastfeeding women vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding women who received COVID-19 mRNA vaccine during pregnancy.
BNT162-01 cohort 13	To assess potentially protective immune responses in immunocompromised adults.
C4591024 (former Safety and immunogenicity in high-risk adults)	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).
C4591021 (former ACCESS/VAC4EU)	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.
C4591038 (former C4591021 substudy)	To assess the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with Comirnaty as well as individuals not vaccinated with a COVID-19 vaccine.
C4591036 (former Pediatric Heart Network study)	To characterise the clinical course, risk factors, long-term effects, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis.
C4591030 (Co-administration study with seasonal influenza vaccine)	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Table 12: Other studies

C4591014	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital due to SARS-CoV-2 infection.
W1235284	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.
W1255886	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.