6 October 2021

COVID-19 vaccine safety update

COMIRNATY

BioNTech Manufacturing GmbH

The safety of Comirnaty is continuously monitored and safety updates are regularly provided to the public. This document outlines the outcomes from the assessment of emerging worldwide safety data carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) (see section 1). It also contains high-level information from the reporting of suspected adverse reactions, which PRAC takes into account in its assessments (see section 2).

This safety update follows the update of 8 September 2021.

Main outcomes from PRAC's latest safety assessment

Erythema multiforme (red spots/patches on the skin) and unusual or decreased feeling in the skin will be added to the product information as side effects of Comirnaty.

The safety updates are published regularly at COVID-19 vaccines: authorised. All published safety updates for Comirnaty are available at Comirnaty: safety updates.

Since its marketing authorisation in the European Union (EU) on 21 December 2020 until 30 September 2021, more than 420 million doses of Comirnaty have been administered in the EU/EEA[1].

1. Updates on safety assessments for Comirnaty

During its meeting held 27 to 30 September 2021, PRAC assessed new safety data (see section 2 'How safety is monitored').

Erythema multiforme

Update to the Comirnaty product information

PRAC continued its assessment of whether erythema multiforme (EM) may be a side effect of Comirnaty.

EM is a skin reaction that causes red spots or patches on the skin, that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings.

124 cases had been spontaneously reported as EM worldwide to EudraVigilance (see section 2) as of 31 July 2021 (around 918 million doses of Comirnaty were estimated to have been administered worldwide by 31 July 2021). In 2 cases EM was ruled out, and in 41 cases the information provided was too limited for assessment. In 26 of the reported cases, EM was reported in close temporal association with the vaccination without apparent plausible alternative explanations for the event. Spontaneously reported cases concern suspected side effects, i.e. medical events that have been observed after vaccination, but which are not necessarily related to or caused by the vaccine.

Based on these case reports and the fact that there is a plausible mechanism for how the vaccine may cause EM, PRAC concluded that the product information should be updated to include EM as a side effect of Comirnaty. The frequency category will be 'unknown frequency', because it is generally difficult to robustly estimate side effect frequencies from

[1] The European Centre for Disease Prevention and Control (ECDC) collects these exposure data from EU Member States as well as from the additional countries of the European Economic Area (EEA) Norway, Iceland and Liechtenstein.

cases of suspected side effects that have been reported spontaneously by healthcare professionals or patients.

Paraesthesia and hypoesthesia

Update to the Comirnaty product information

PRAC concluded that paraesthesia (unusual feeling in the skin, such as tingling or a crawling sensation) and hypoesthesia (decreased feeling or sensitivity in the skin) should be added to the product information as side effects of Comirnaty.

This conclusion was based on a total of 21,793 paraesthesia and/or hypoesthesia cases spontaneously reported worldwide to EudraVigilance (see section 2) by 12 August 2021 (around 1,220 million doses of Comirnaty were estimated to have been administered worldwide by 31 August 2021). Spontaneously reported cases concern suspected side effects, i.e. medical events that have been observed after vaccination, but which are not necessarily related to or caused by the vaccine. Of the reported cases of paraesthesia or hypoesthesia, approximately 75% occurred within the day after vaccination.

Other events: Asthenia, lethargy, decreased appetite and (nocturnal) hyperhidrosis

Update to the Comirnaty product information

In the context of the review of clinical trial data by the Committee for Medicinal Products for Human Use (CHMP)[2], asthenia (lack of energy or strength), lethargy (state of indifference and inactivity), decreased appetite and (nocturnal [nighttime]) hyperhidrosis (excessive sweating) have been added as side effects to the product information of Comirnaty. The frequency category for these events is 'uncommon' (i.e. occurring in less than 1 in 100 persons).

Menstrual disorders

No evidence for causal relationship with Comirnaty

PRAC assessed cases reported as menstrual disorders occurring after vaccination with Comirnaty.

Until 30 August 2021, a total of 16,263 cases had been reported worldwide (16,226 as spontaneous reports; 6,118 as serious), of which 1,665 (10.2%) were medically confirmed by a healthcare professional as menstrual disorder (around 1,220 million doses of Comirnaty were estimated to have been administered worldwide by 31 August 2021). Spontaneously reported cases concern suspected side effects, i.e. medical

[2] See safety update for Comirnaty of 14 July 2021

events that have been observed after vaccination, but which are not necessarily related to or caused by the vaccine.

The assessment of all cases included an analysis of the type of symptoms and their time to onset; no specific pattern of menstrual cycle disturbances could be identified. In about half of the cases, past or current relevant medical conditions or concurrent medication were considered plausible explanations for menstrual disorders. An observed-to-expected (O/E) analysis for the 6,050 cases reported as 'heavy menstrual bleeding' (which was the most frequently reported disorder at 34.7%) resulted in an O/E ratio below 1; this means the number of cases reported after vaccination in relevant time windows was below the number of events expected to occur in an unvaccinated female population of the same size (based on observational data collected from the general population).

Based on the assessment of all data, PRAC concluded that there is currently no evidence suggesting a causal relationship of menstrual disorders with Comirnaty.

Menstrual disorders are very common in the general population and can occur without an underlying medical condition. Causes can range from stress and tiredness to conditions such as fibroids and endometriosis.

An assessment carried out in August 2021 by the Medicines & Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) also concluded that the number of case reports in the UK were low in relation to both the number of vaccinated women and how common menstrual disorders are generally, that the symptoms were transient and that the data did not support a causal link between changes to menstrual periods and the COVID-19 vaccines available in the UK, including Comirnaty[3].

Glomerulonephritis and nephrotic syndrome

Close monitoring continues

Following a small number of cases after vaccination with Comirnaty reported in the medical literature[4], PRAC continued its assessment of whether glomerulonephritis (inflammation of tiny filters in the kidneys)

[3] For the latest UK data, see Coronavirus vaccine – weekly summary of Yellow Card reporting

[4] D'Agati et al. Minimal change disease and acute kidney injury following the Pfizer-BioNTech COVID-19 vaccine. Kidney Int. 2021.; Lebedev et al. Minimal change disease following the Pfizer-BioNTech COVID-19 vaccine. Am J Kidney Dis. 2021.; Kervella et al. Minimal change disease relapse following SARS-CoV-2 mRNA vaccine. Kidney Int. 2021.; Komaba et al. Relapse of minimal change disease following the Pfizer-BioNTech COVID-19 Vaccine, Am J Kidney Dis. 2021.; Maas et al. An additional case of minimal change disease following the Pfizer-BioNTech COVID-19 Vaccine. Am J Kidney Dis. 2021.; Mancianiti et al. Minimal change disease following vaccination for SARS-CoV-2. Journal of Nephrology. 2021.; Rahim et al. A case of gross hematuria and IgA nephropathy flare-up following SARS-CoV-2 vaccination. Kidney Int. 2021.; Schwotzer et al. Letter regarding "Minimal change disease relapse following SARS-CoV-2 mRNA vaccine". Kidney Int. 2021.; Tan et al. Is COVID-19 vaccination unmasking glomerulonephritis? Kidney Int. 2021.

and nephrotic syndrome (kidney disorder causing the kidneys to leak too much protein in the urine) may be side effects of Comirnaty.

PRAC assessed 89 cases reported as glomerulonephritis or nephrotic syndrome worldwide to EudraVigilance (see section 2) by 31 July 2021 (around 918 million doses of Comirnaty were estimated to have been administered worldwide by 31 July 2021). Spontaneously reported cases concern suspected side effects, i.e. medical events that have been observed after vaccination, but which are not necessarily related to or caused by the vaccine. After analysis of the cases, no particular patterns could be identified, and information regarding medical history, confounding conditions or risk factors was found to be lacking in many cases.

PRAC concluded that the available data did not establish a causal relationship of glomerulonephritis or nephrotic syndrome with Comirnaty and that an update to the product information of Comirnaty is not warranted at present. However, the topic remains under close monitoring.

PRAC encourages all healthcare professionals and patients to report any cases of glomerulonephritis or nephrotic syndrome occurring in people after vaccination (see section 2). Affected patients may present with bloody or foamy urine, oedema (swelling especially of the eyelids, feet or abdomen), or fatigue.

2. How safety is monitored

As for all COVID-19 vaccines, relevant new information emerging on Comirnaty is collected and promptly reviewed. This is in line with the pharmacovigilance plan for COVID-19 vaccines of the EU regulatory network (comprising the regulatory bodies of the EU Member States, EMA and the European Commission).

Summary safety reports

The pharmacovigilance plan for COVID-19 vaccines includes Monthly Summary Safety Reports (MSSRs) which are compiled by the marketing authorisation holders to support timely and continuous benefit-risk evaluations for COVID-19 vaccines used during the pandemic. MSSRs are intended to be compiled for at least the first six months of marketing (afterwards, pandemic summary safety reports may cover time periods longer than a month). These reports complement the submission of Periodic Safety Update Reports (PSURs).

Case reports of suspected side effects

Collecting reports of medical events and problems that occur following the use of a medicine, and therefore might be side effects, is one of the pillars of the EU safety monitoring system. Healthcare professionals and vaccinated individuals are encouraged to report to their national

competent authorities all suspected side effects individuals may have experienced after receiving a vaccine even if it is unclear whether the vaccine was the cause. For more information on how to report, including the importance of detailing the vaccine product name and the batch, see Reporting suspected side effects.

These spontaneous reports are collected in EudraVigilance, the EU database used for monitoring and analysing suspected side effects. Publicly available information can be accessed via EudraVigilance – European database of suspected drug reaction reports in all EU/EEA languages. Search for "COVID-19 mRNA Vaccine PFIZER-BIONTECH (Tozinameran)" to see all suspected side effect cases reported for Comirnaty.

As of 30 September 2021, a total of 361,767 cases of suspected side effects with Comirnaty were spontaneously reported to EudraVigilance from EU/EEA countries; 5,113 of these reported a fatal outcome[5,6]. By the same date more than 420 million doses of Comirnaty had been given to people in the EU/EEA[7].

These reports describe suspected side effects in individuals, i.e. medical events observed following the use of a vaccine. The fact that someone has had a medical issue or died after vaccination does not necessarily mean that this was caused by the vaccine. This may have been caused, for example, by health problems not related to the vaccination.

The EU regulatory network continuously monitors EudraVigilance to detect any new safety issues. EudraVigilance relies on individual healthcare professionals and patients to report their own experience. The monitoring detects unusual or unexpected patterns in the reports received for further investigation and risk assessment. EMA's detailed assessments take into account all available data from all sources to draw a robust conclusion on the safety of the vaccine. These data include clinical trial results, reports of suspected side effects in EudraVigilance, epidemiological studies monitoring the safety of the vaccine, toxicological investigations and any other relevant information.

[5] These figures have been calculated excluding cases reported from Northern Ireland (EU reporting requirements for suspected adverse reactions to EudraVigilance apply to Northern Ireland in accordance with the Protocol on Ireland/Northern Ireland).
[6] Source: EudraVigilance. These figures cannot be extracted directly from the public database of suspected adverse reactions, which groups information per type of side effects. As more than one suspected side effect may have been included in a single case report, the total number of side effects will never match the number of individual cases. Similarly, this public database does not provide the total number of cases reported with a fatal outcome.
[7] The European Centre for Disease Prevention and Control (ECDC) collects these exposure data from EU Member States as well as from the additional countries of the European Economic Area (EEA) Norway, Iceland and Liechtenstein.

Planned and ongoing studies

The company that markets Comirnaty will continue to provide results from the main clinical trial, which is ongoing for up to two years. It will also conduct additional studies to monitor the safety and effectiveness of the vaccine as it is used in vaccination campaigns and other clinical practice. For the list of planned and ongoing safety studies for Comirnaty, see the risk management plan.

A paediatric investigation plan (PIP) for Comirnaty is in place. This describes how the company collects data on the vaccine's efficacy and safety for its use in children.

In addition, EMA is coordinating observational studies in EU Member States looking at real-world data from clinical practice to monitor the safety and effectiveness of COVID-19 vaccines, including in pregnant women.

3. Other information for Comirnaty

Comirnaty is a vaccine that was authorised in the EU on 21 December 2020 to prevent COVID-19 when infected with the coronavirus SARS-CoV-2. COVID-19 is a potentially severe disease that may result in death. The initial marketing authorisation was for use in people aged 16 years and older; on 31 May 2021, the marketing authorisation was extended to use in individuals aged 12 years and older.

Comirnaty contains a molecule called mRNA, which the body uses to temporarily produce the SARS-CoV-2 spike protein. The mRNA is broken down shortly after vaccination. The spike protein does not cause COVID-19.

Before Comirnaty was granted an EU marketing authorisation, the efficacy and safety of the vaccine were assessed through pre-clinical studies and large clinical trials. More than 18,000 participants had been given the vaccine in clinical trials.

Like all medicines, this vaccine can cause side effects, although not everybody will experience them. The most common side effects known for Comirnaty are usually mild or moderate and get better within a few days after vaccination.

More information on how Comirnaty works and its use is available in all EU/EEA languages in the medicine overview. This includes information on use in pregnant and breastfeeding women and immunocompromised individuals.

The full product information with the summary of product characteristics and the package leaflet is also available in all EU/EEA languages.

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