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COVID-19 vaccine safety update

SPIKEVAX

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The safety of Spikevax 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) will be added to the product information as a side effect of Spikevax.

The safety updates are published regularly at [COVID-19 vaccines: authorised](#). All published safety updates for Spikevax (previously known as COVID-19 Vaccine Moderna) are available at [Spikevax: safety updates](#).

Since its marketing authorisation in the European Union (EU) on 6 January 2021 until 30 September 2021, more than 59.8 million doses of Spikevax have been administered in the EU/EEA¹.



1. Updates on safety assessments for Spikevax

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 Spikevax product information

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

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.

143 cases had been spontaneously reported as EM worldwide to EudraVigilance (see section 2) as of 31 July 2021 (around 207 million doses of Spikevax were estimated to have been administered worldwide by 31 July 2021). Of these, 29 were assessed as confirmed reports of EM; 5 of these were considered to be probably causally related to Spikevax and 20 as possibly causally related to Spikevax. This was determined based on a plausible time to onset of the adverse event following vaccination, the absence of alternative explanations and the level of information available in the case reports. 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 erythema multiforme as a side effect of Spikevax. The frequency category will be 'unknown'

¹ The [European Centre for Disease Prevention and Control \(ECDC\)](https://ecdc.europa.eu/en/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.

frequency', because it is generally difficult to robustly estimate side effect frequencies from cases of suspected side effects that have been reported spontaneously by healthcare professionals or patients.

Menstrual disorders

No evidence for causal relationship with Spikevax

PRAC assessed cases reported as menstrual disorders occurring after vaccination with Spikevax as well as a review of the scientific literature.

Until 31 August 2021, a total of 3,619 cases had been reported spontaneously worldwide (118 concerned post-menopausal bleeding), of which 829 (22.9%) were medically confirmed by a healthcare professional as menstrual disorder (117 as serious) (around 230 million doses of Spikevax 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.

The assessment of all spontaneously reported cases included an analysis of the type of symptoms, their time to onset and duration, as well as concomitant treatment and medical history/current conditions; no specific pattern of menstrual cycle disturbances could be identified. The event duration was short, with an average of 10.3 days and a median of 5.0 days (range 0-179). Observed-to-expected (O/E) analyses for pre- and postmenopausal women resulted in O/E ratios substantially below 1; this means the numbers of cases reported after vaccination in relevant time windows were below the numbers of such events expected to occur in the unvaccinated female populations of the same size (based on observational data collected from the general population), even when assuming that all reported cases would be assessed as possibly causally related. In addition, no statistical differences in reports of menstrual disorder between the vaccinated and unvaccinated groups could be identified from clinical trial data.

PRAC also considered the assessment carried out in August 2021 by the Medicines & Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK), which 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 Spikevax².

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

² For the latest UK data, see [Coronavirus vaccine – weekly summary of Yellow Card reporting](#)

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.

Glomerulonephritis and nephrotic syndrome

Close monitoring continues

Following a small number of cases after vaccination with Spikevax reported in the medical literature³, PRAC continued their assessment of whether glomerulonephritis (inflammation of tiny filters in the kidneys) and nephrotic syndrome (kidney disorder causing the kidneys to leak too much protein in the urine) may be side effects of Spikevax.

PRAC assessed 33 cases which had been spontaneously reported as glomerulonephritis or nephrotic syndrome worldwide to EudraVigilance (see section 2). Of these, 11 cases were assessed as possibly causally related to Spikevax based on a plausible temporal association. The relapsing/remitting forms of this type of disease are common and the cause of relapse or new-onset disease can often not be determined. The remaining cases were considered unlikely to be causally related to Spikevax or could not be assessed due to limited information in the case reports. An observed-to-expected (O/E) analysis (which looked at the number of cases reported worldwide in relation to the number of such events expected to occur in the unvaccinated population of the same size [based on observational data collected from the general population]) did not show statistically significant increases.

PRAC concluded that the currently available data were not sufficient to establish a causal relationship of glomerulonephritis or nephrotic syndrome with Spikevax. 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 Spikevax is collected and promptly reviewed. This is in line with the

³ Anderegg et al. De novo vasculitis after mRNA-1273 (Moderna) vaccination. *Kidney Int.* 1 Jun 2021.; Holzworth et al. Minimal change disease following the Moderna mRNA-1273 SARS-CoV-2 vaccine *Kidney Int.* 2021; 100: 463-464.; Kudose et al. Histologic correlates of gross hematuria following Moderna COVID-19 vaccine in patients with IgA nephropathy. *Kidney international.* 16 June 2021.; Negrea & Rovin. Gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 in 2 patients with IgA nephropathy. *Kidney Int.* 2021; 99: 1487.; Sekar et al. ANCA glomerulonephritis after the Moderna COVID-19 vaccination. *Kidney international.* 31 May 2021.

[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 MODERNA (CX-024414)” to see all suspected side effect cases reported for Spikevax.

As of 30 September 2021, a total of 80,486 cases of suspected side effects with Spikevax were spontaneously reported to EudraVigilance from EU/EEA countries; 495 of these reported a fatal outcome^{4,5}. By the same

⁴ 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).

⁵ 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.

date, more than 59.8 million doses of Spikevax had been given to people in the EU/EEA⁶.

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.

Planned and ongoing studies

The company that markets Spikevax 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 Spikevax, see the [risk management plan](#).

A [paediatric investigation plan](#) (PIP) for Spikevax 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 Spikevax

Spikevax (previously known as COVID-19 Vaccine Moderna) is a vaccine that was authorised in the EU on 6 January 2021 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

⁶ 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.

authorisation was for use in people aged 18 years and older; on 23 July 2021, the marketing authorisation was extended to use in individuals aged 12 years and older.

Spikevax 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 Spikevax 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 14,000 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 Spikevax are usually mild or moderate and get better within a few days after vaccination.

More information on how Spikevax 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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