EUROPEAN MEDICINES AGENCY
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COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)
COVID-19 Vaccine Janssen (Janssen-Cilag International NV)
Nuvaxovid (Novavax CZ, a.s.)
Spikevax (Moderna Biotech Spain, S.L.)
Vaxzevria (AstraZeneca AB)

Marketing authorisation withdrawal

Vaxzevria and Jcovden (previously COVID-19 Vaccine Janssen) were withdrawn from the EU market at the request of the marketing authorisation holders for commercial reasons. The withdrawals do not affect the information provided in this safety update.

The safety of authorised COVID-19 vaccines is continuously monitored, and updated information is regularly provided to the public.

Safety updates outline the outcomes from assessments of emerging worldwide safety data carried out mainly by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) (section 1). They also outline how safety is monitored and contain high-level information on suspected adverse reaction reports, which PRAC takes into account in its assessments (section 2).

This safety update follows the update of 17 February 2022 and reflects the main assessment outcomes of the PRAC meetings held 7 to 10 March 2022.

EMA confirms that the benefits of all currently authorised COVID-19 vaccines continue to outweigh their side effects, given the risk of COVID-19 illness and related complications, including hospitalisation and death.

[1] This document was updated on 7 May 2024 and 9 August 2024 following the withdrawals of Vaxzevria and Jcovden (previously COVID-19 Vaccine Janssen), respectively.

Key messages from the latest safety assessments

COVID-19 Vaccine Janssen

PRAC recommends updating the product information to include cutaneous small vessel vasculitis (inflammation of blood vessels in the skin) as a new side effect of COVID-19 Vaccine Janssen.

Spikevax

PRAC recommends updating the product information with a warning to reflect the potential of flare-ups of capillary leak syndrome (leakage of fluid from blood vessels) following vaccination with Spikevax, in patients who have a medical history of this extremely rare condition.

1. Latest safety assessments

Comirnaty (BioNTech Manufacturing GmbH)

About 592 million doses of Comirnaty in adults and 25 million doses of Comirnaty in children and adolescents (below 18 years of age) were administered in the EU/EEA from authorisation to 28 February 2022.[2]

Capillary leak syndrome (CLS)

No update to the product information required

An assessment of whether vaccination with Comirnaty can cause capillary leak syndrome (CLS) has been completed. PRAC has concluded that there are currently insufficient data to support an update of the product information.

In the general population, CLS is an extremely rare, serious condition that causes fluid leakage from small blood vessels (capillaries), resulting in swelling mainly in the arms and legs, low blood pressure, thickening of the blood and low blood levels of albumin (an important blood protein). The

[2] 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.

assessment considered spontaneously reported cases of 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.

Further information can be found in the PRAC highlights of March 2022.

Information on how Comirnaty works is provided in the medicine overview (in all EU/EEA languages). Full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages).

COVID-19 Vaccine Janssen (Janssen-Cilag International NV)

About 19.2 million doses of COVID-19 Vaccine Janssen were administered to adults in the EU/EEA from authorisation to 28 February 2022.[2]

Cutaneous small vessel vasculitis

Update to the product information

PRAC has recommended that small vessel vasculitis with cutaneous manifestations (inflammation of blood vessels in the skin which may result in a rash, pointed or flat, red spots under the skin's surface and bruising) should be added to the product information of COVID-19 Vaccine Janssen as a possible side effect of unknown frequency. Small vessel vasculitis can be caused by viral or bacterial infections as well as by medicines and vaccines. Generally, manifestations of the disease spontaneously resolve over time with appropriate supportive care.

The recommendation to update the product information should include the side effect with a frequency category of 'unknown frequency'; 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.

PRAC had previously recommended adding cutaneous small vessel vasculitis to the product information as a possible side effect of COVID-19 Vaccine Janssen (see safety update of 8 September 2021), However, a re-assessment was requested by the marketing authorisation holder. Following this re-assessment, PRAC has maintained its conclusion. The assessment considered spontaneously reported cases of 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.

Further information can be found in the PRAC highlights of March 2022.

Myocardial infarction

Assessment started

PRAC is aware of the results of an epidemiological study based on French national databases and posted on the EPI-PHARE website suggesting a slightly increased risk for myocardial infarction (heart attack) with COVID-19 Vaccine Janssen and within 3 weeks of first dose.

PRAC will collect and assess all available data, including data from the marketing authorisation holder, to determine whether myocardial infarction may be caused by COVID-19 Vaccine Janssen.

Information on how COVID-19 Vaccine Janssen works is provided in the medicine overview (in all EU/EEA languages); full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages). The product information will be updated to reflect the latest safety assessment outcomes.

Nuvaxovid (Novavax CZ, a.s.)

There are no safety updates for Nuvaxovid. By 28 February 2022, the vaccine was not yet in use in the EU/EEA.[2] Information on how Nuvaxovid works is provided in the medicine overview (in all EU/EEA languages); full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages).

Spikevax (Moderna Biotech Spain, S.L.)

About 150 million doses of Spikevax in adults and 1.9 million doses of Spikevax in children and adolescents (below 18 years of age) were administered in the EU/EEA from authorisation to 28 February 2022.[2]

Capillary leak syndrome (CLS)

Update to the product information

An assessment of whether vaccination with Spikevax can cause capillary leak syndrome (CLS) has been completed. PRAC has recommended updating the product information with a warning to reflect the potential

occurrence of CLS flare-up following vaccination with Spikevax in patients who have a history of this extremely rare condition. The assessment considered spontaneously reported cases of 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

In the general population, CLS is an extremely rare, serious condition that causes fluid leakage from small blood vessels (capillaries), resulting in swelling mainly in the arms and legs, low blood pressure, thickening of the blood and low blood levels of albumin (an important blood protein).

Further information can be found in the PRAC highlights of March 2022.

A few cases of capillary leak syndrome (CLS) flare-up (causing fluid leakage from small blood vessels (capillaries) resulting in rapid swelling of the arms and legs, sudden weight gain and feeling faint, low blood pressure) have been reported following vaccination with Spikevax. If you have previously had episodes of CLS, talk to a doctor before you are given Spikevax.

Information on how Spikevax works is provided in the medicine overview (in all EU/EEA languages). Full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages). The product information will be updated to reflect the latest safety assessment outcomes.

Vaxzevria (AstraZeneca AB)

About 69 million doses of Vaxzevria were administered to adults in the EU/EEA from authorisation to 28 February 2022.[2]

Myocardial infarction, pulmonary embolism and thromboses

Assessment started

PRAC is aware of results of an epidemiological study based on French national databases and posted on the EPI-PHARE website which suggest a slightly increased risk of myocardial infarction (heart attack) and pulmonary embolism (a blocked blood vessel in the lungs) following vaccination with

Vaxzevria. In addition, a slightly increased risk of venous and/or arterial thromboses (blood clots) has been noted in other published studies.[3]

PRAC will collect and assess all available data, including data from the marketing authorisation holder, to determine whether the conditions may be caused by Vaxzevria.

Information on how Vaxzevria works is provided in the medicine overview (in all EU/EEA languages); full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages).

2. How safety is monitored

Before COVID-19 vaccines were granted EU marketing authorisation, the efficacy and safety of the vaccines were assessed in pre-clinical studies and large clinical trials.

All relevant new information emerging worldwide on the vaccines since marketing authorisation is collected and promptly assessed. 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).

EMA's detailed assessments take into account available data from all sources to draw robust conclusions on the safety of the vaccines. These data include clinical trial results, reports of suspected side effects, epidemiological studies monitoring the safety of the vaccine, toxicological investigations and any other relevant information.

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 in the first months of marketing. Afterwards, summary safety reports may cover time periods longer than a month or not be necessary anymore. summary safety reports complement periodic safety update reports (PSURs).

[3] Including: Whiteley et al. https://doi.org/10.1371/journal.pmed.1003926 and Hippisley-Cox et al. https://doi.org/10.1136/bmj.n1931

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).

As of 28 February 2022, EudraVigilance contained the following figures:

- Comirnaty: a total of 636,973 cases of suspected side effects spontaneously reported from EU/EEA countries; 7,411 of these reported a fatal outcome[4,5] (by the same date about 617 million doses of Comirnaty had been given to people in the EU/EEA[2]);
- COVID-19 Vaccine Janssen: a total of 43,650 cases of suspected side effects spontaneously reported from EU/EEA countries; 294 of these reported a fatal outcome[4,5] (by the same date, about 19.2 million doses of COVID-19 Vaccine Janssen had been administered to people in the EU/EEA[2]);
- Spikevax: a total of 171,454 cases of suspected side effects spontaneously reported from EU/EEA countries; 931 of these reported a fatal outcome[4,5] (by the same date, about 152 million doses of Spikevax had been given to people in the EU/EEA[2]);
- Vaxzevria: a total of 256,038 cases of suspected side effects spontaneously reported from EU/EEA countries; 1,485 of these reported a fatal outcome[4,5] (by the same date, about 69 million doses of Vaxzevria had been given to people in the EU/EEA[2]).

These reports describe suspected side effects in individuals, i.e. medical events observed following the use of a vaccine. The fact

[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 effect. 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.

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.

Planned and ongoing studies

The companies that market COVID-19 vaccines continue to provide results from ongoing clinical trials. They also conduct additional studies to monitor the safety and effectiveness of the vaccines as they are used in vaccination campaigns and other clinical practice. For the list of planned and ongoing safety studies with COVID-19 vaccines, see the respective risk management plan: Comirnaty, COVID-19 Vaccine Janssen, Nuvaxovid, Spikevax, and Vaxzevria.

A paediatric investigation plan (PIP) is in place for each authorised COVID-19 vaccine: Comirnaty, COVID-19 Vaccine Janssen, Nuvaxovid, Spikevax, and Vaxzevria. The PIP describes how the company will collect data on the vaccine's efficacy and safety for its potential use in children. Two vaccines, Comirnaty and Spikevax, are authorised for 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.

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