



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)

COVID-19 Vaccine Valneva (Valneva Austria GmbH)

Jcovden (Janssen-Cilag International NV)

Nuvaxovid (Novavax CZ, a.s.)

Spikevax (Moderna Biotech Spain, S.L.)

Vaxzevria (AstraZeneca AB)

Update as of 1 December 2023

COVID-19 Vaccine Valneva was withdrawn from the EU market at the request of the company for commercial reasons. The withdrawal does 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 6 October 2022 and reflects the main assessment outcomes of the PRAC meeting held 24 to 27 October 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 1 December 2023 to include a statement on the withdrawal of COVID-19 Vaccine Valneva.

Key messages from the latest safety assessments

For Comirnaty and Spikevax, an update to the product information has been recommended to add heavy menstrual bleeding as a side effect.

For Spikevax, a further update to the product information has been recommended to include urticaria as an uncommon side effect (i.e., occurring in less than 1 in 100 persons).

1. Latest safety assessments

Comirnaty (BioNTech Manufacturing GmbH)

Heavy menstrual bleeding

Update to the product information

The PRAC has now concluded its assessment of heavy menstrual bleeding (see [PRAC highlights, October 2022](#)). The Committee has recommended that heavy menstrual bleeding should be added to the Comirnaty product information as a side effect of unknown frequency.

The conclusion was based on evidence including cases reported during clinical trials, observational studies, intensified post-marketing surveillance activities and spontaneously reported cases by patients and healthcare professionals, including from European countries, present in EudraVigilance. The assessment included almost 9,000 worldwide reports of heavy menstrual bleeding with either Comirnaty or Spikevax (both mRNA vaccines).

The frequency category assigned is 'not known', as it is generally difficult to robustly estimate side effect frequencies from spontaneously reported cases of suspected side effects. In general, cases reported spontaneously by a patient or healthcare professional 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.

Heavy menstrual bleeding (heavy periods) may be defined as bleeding characterised by an increased volume and/or duration which interferes with the person's physical, social, emotional and material quality of life. Cases of heavy menstrual bleeding have been reported after the first, second and booster doses of Comirnaty. A small number of cases involved positive

rechallenge (where heavy menstrual bleeding was seen after the initial vaccination and occurred again after a second dose). A positive rechallenge may indicate that a medicine may have caused the side effect in question.

The available data reviewed involved cases that were mostly [non-serious](#) and temporary.

After reviewing the data, the Committee concluded that there is at least a reasonable possibility that heavy menstrual bleeding is causally associated with Comirnaty and therefore recommended updating the product information.

Menstrual disorders in general are quite common and they can occur for a wide range of reasons. This includes some underlying medical conditions. Any person who experiences postmenopausal bleeding or is concerned about a change in menstruation should consult their doctor.

There is no evidence to suggest that menstrual changes experienced by some people following vaccination have any impact on fertility.

With regard to the effects of COVID-19 vaccination on pregnancy in general, [several studies](#) involving around 65,000 pregnancies at different stages did not find any sign of an increased risk of pregnancy complications, miscarriages, preterm births or adverse effects in the unborn babies following mRNA COVID-19 vaccination.

PRAC will continue to monitor cases of heavy menstrual bleeding and will communicate further if new recommendations are warranted.

Healthcare professionals and patients are encouraged to continue to report cases of menstrual disorders following COVID-19 vaccination to their national authorities.



About 672 million doses of Comirnaty, including about 55.8 million doses in children and adolescents (below 18 years of age), were administered in the EU/EEA from authorisation to 12 October 2022.

Additionally, over **7 million doses of adapted Comirnaty vaccines** (bivalent) have also been administered in adults.²

The initial conditional marketing authorisation for Comirnaty in the EU was issued on 21 December 2020; following an [assessment process](#), it was [converted into a standard marketing authorisation](#) on 10 October 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).

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.

COVID-19 Vaccine (inactivated, adjuvanted) Valneva (Valneva Austria GmbH)

There are no safety updates for COVID-19 Vaccine (inactivated, adjuvanted) Valneva.



About 2,400 doses of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in adults were administered in the EU/EEA from authorisation to 12 October 2022.²

The initial, standard marketing authorisation for COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the EU was issued on 24 June 2022. Information on how COVID-19 Vaccine (inactivated, adjuvanted) Valneva 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).

Jcovden (Janssen-Cilag International NV)

There are no safety updates for Jcovden.



About 19.4 million doses of Jcovden in adults were administered in the EU/EEA from authorisation to 12 October 2022.³

The initial conditional marketing authorisation for Jcovden (previously COVID-19 Vaccine Janssen) in the EU was issued on 11 March 2021. Information on how Jcovden 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).

Nuvaxovid (Novavax CZ, a.s.)

There are no safety updates for Nuvaxovid.

³ 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.



About 291,000 doses of Nuvaxovid in adults were administered in the EU/EEA from authorisation to 12 October 2022.²

The initial conditional marketing authorisation for Nuvaxovid in the EU was issued on 20 December 2021. 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.)

Heavy menstrual bleeding

Update to the product information

The PRAC has now concluded its assessment of heavy menstrual bleeding (see [PRAC highlights, October 2022](#)). The Committee has recommended that heavy menstrual bleeding should be added to the Spikevax product information as a side effect of unknown frequency.

The conclusion was based on evidence including cases reported during clinical trials, observational studies, intensified post-marketing surveillance activities and spontaneously reported cases by patients and healthcare professionals, including from European countries, present in EudraVigilance. The assessment included almost 9,000 worldwide reports of heavy menstrual bleeding with either Comirnaty or Spikevax (both mRNA vaccines).

The frequency category assigned is 'not known', as it is generally difficult to robustly estimate side effect frequencies from spontaneously reported cases of suspected side effects. In general, cases reported spontaneously by a patient or healthcare professional 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.

Heavy menstrual bleeding (heavy periods) may be defined as bleeding characterised by an increased volume and/or duration which interferes with the person's physical, social, emotional and material quality of life. Cases of heavy menstrual bleeding have been reported after the first, second and booster doses of Spikevax. A small number of cases involved positive rechallenge (where heavy menstrual bleeding was seen after the initial vaccination and occurred again after a second dose). A positive rechallenge may indicate that a medicine may have caused the side effect in question.

The available data reviewed involved cases that were mostly [non-serious](#) and temporary.

After reviewing the data, the Committee concluded that there is at least a reasonable possibility that heavy menstrual bleeding is causally associated with Spikevax and therefore recommended updating the product information.

Menstrual disorders in general are quite common and they can occur for a wide range of reasons. This includes some underlying medical conditions. Any person who experiences postmenopausal bleeding or is concerned about a change in menstruation should consult their doctor.

There is no evidence to suggest that menstrual changes experienced by some people following vaccination have any impact on fertility.

With regard to the effects of COVID-19 vaccination on pregnancy in general, [several studies](#) involving around 65,000 pregnancies at different stages did not find any sign of an increased risk of pregnancy complications, miscarriages, preterm births or adverse effects in the unborn babies following mRNA COVID-19 vaccination.

PRAC will continue to monitor cases of heavy menstrual bleeding and will communicate further if new recommendations are warranted.

Healthcare professionals and patients are encouraged to continue to report cases of menstrual disorders following COVID-19 vaccination to their national authorities.

Urticaria

Update to the product information

The PRAC concluded an assessment of the hypersensitivity reaction urticaria (hives [raised, red and itchy skin rash]) with Spikevax. After reviewing the data, the Committee concluded that there is at least a reasonable possibility that urticaria is causally associated with Spikevax and therefore recommended updating the product information.

The Committee recommended that urticaria should be added to the product information as a side effect of uncommon frequency (occurring in less than 1 in 100 people). Urticaria has been observed with either acute onset (within a few days after vaccination) or delayed onset (up to approximately two weeks after vaccination).



About 158 million doses of Spikevax, including about 3.1 million doses in children and adolescents (below 18 years of age), were administered in the EU/EEA from authorisation to 12 October 2022.

Additionally, over **180,000 doses of adapted Spikevax vaccines** (bivalent) have also been administered in adults.⁴

⁴ 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.

The initial conditional marketing authorisation for Spikevax (previously COVID-19 Vaccine Moderna) in the EU was issued on 6 January 2021; following an [assessment process](#), it was [converted into a standard marketing authorisation](#) on 3 October 2022.

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).

Vaxzevria (AstraZeneca AB)

There are no safety updates for Vaxzevria.



About 69 million doses of Vaxzevria in adults were administered in the EU/EEA from authorisation to 12 October 2022.⁵

The initial conditional marketing authorisation for Vaxzevria (previously COVID-19 Vaccine AstraZeneca) in the EU was issued on 29 January 2021; following an assessment process, it was converted into a standard marketing authorisation on 31 October 2022.

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).

⁵ 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.

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 all 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 may not be necessary anymore. Summary safety reports complement [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).

As of 26 October 2022, EudraVigilance contained the following:

- Comirnaty: a total of 948,424 cases (plus 1,661 cases relating to Comirnaty bivalent vaccines) of suspected side effects spontaneously

reported from EU/EEA countries; 8,321 of these reported a fatal outcome (plus 21 relating to Comirnaty bivalent vaccines)^{6,7} (by 12 October 2022, about 672 million doses of Comirnaty had been given to people in the EU/EEA – plus over 7 million doses of Comirnaty bivalent vaccines⁸);

- COVID-19 Vaccine (inactivated, adjuvanted) Valneva: 1 case of suspected side effects spontaneously reported from EU/EEA countries; there was no fatal outcome^{5,6} (by 12 October 2022, about 2,400 doses of COVID-19 Vaccine had been given to people in the EU/EEA⁷);
- Jcovden: a total of 58,226 cases of suspected side effects spontaneously reported from EU/EEA countries; 336 of these reported a fatal outcome^{5,6} (by 12 October 2022, about 19.4 million doses of Jcovden had been administered to people in the EU/EEA⁷);
- Nuvaxovid: a total of 1,398 cases of suspected side effects spontaneously reported from EU/EEA countries; there was no fatal outcome^{5,6} (by 12 October 2022, about 291,000 doses of Nuvaxovid had been administered to people in the EU/EEA⁷);
- Spikevax: a total of 263,598 cases (plus 1,507 cases relating to Spikevax bivalent vaccines) of suspected side effects spontaneously reported from EU/EEA countries; 1,146 of these reported a fatal outcome (plus 5 relating to Spikevax bivalent vaccines)^{5,6} (by 12 October 2022, about 158 million doses of Spikevax had been given to people in the EU/EEA - plus over 180,000 doses of Spikevax bivalent vaccines⁷);
- Vaxzevria: a total of 320,860 cases of suspected side effects spontaneously reported from EU/EEA countries; 1,576 of these reported a fatal outcome^{5,6} (by 12 October 2022, about 69 million doses of Vaxzevria had been given to people in the EU/EEA⁷).

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.

⁶ 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).

⁷ 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.

⁸ 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.

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 (RMP): [Comirnaty](#), [COVID-19 Vaccine \(inactivated, adjuvanted\)](#), [Valneva](#), [Jcovden](#), [Nuvaxovid](#), [Spikevax](#) and [Vaxzevria](#).

A [paediatric investigation plan](#) (PIP) is in place for each authorised COVID-19 vaccine: [Comirnaty](#), [COVID-19 Vaccine \(inactivated, adjuvanted\)](#), [Valneva](#), [Jcovden](#), [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 and adolescents (below 18 years of age). Three vaccines are authorised in the EU for use in children and adolescents: Comirnaty (as of 6 months), Nuvaxovid (as of 12 years) and Spikevax (as of 6 months).

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

European Medicines Agency

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact

Telephone +31 (0)88 781 6000

