



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 September 2022 Rev.1¹

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COVID-19 Vaccine Valneva was withdrawn from the EU market at the request of the company for commercial reasons.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 14 July 2022 (with new information added on 3 August 2022) and reflects the main assessment outcomes of the PRAC meeting held 29 August to 01 September 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

An update to the product information of Comirnaty is recommended to reflect that the risk of myocarditis and pericarditis seems to be lower in children aged 5 to 11 years than in those aged 12 to 17 years.

1. Latest safety assessments

Corneal graft rejection (CGR)

Available evidence does not support a causal relationship of CGR with Comirnaty, Spikevax or Vaxzevria

In April 2022, PRAC started an assessment of corneal graft rejection (CGR) to establish whether it may be a side effect of COVID-19 vaccines (see [safety update of April 2022](#)). CGR occurs when the body's immune system mistakenly attacks the donor cornea (the transparent layer in front of the eye) that has replaced a damaged or diseased cornea.

PRAC has now concluded that the available evidence does not support a causal relationship between Comirnaty, Spikevax or Vaxzevria and CGR.

PRAC assessed all available data, including the scientific literature and cases of CGR reported to EudraVigilance (see section 2) for each of the three vaccines individually (no cases were reported for the other EU-authorised COVID-19 vaccines). PRAC's conclusion was based on a number of common factors, including the small number of cases reported after vaccination (fewer than 100 cases worldwide for all three vaccines together) and the presence of CGR risk factors in many of the concerned patients (e.g. history of previous graft failure, prior eye surgery, or history of eye infection). Corneal graft procedure is one of the most commonly performed transplants and symptoms of graft rejection generally occur in about 10% of corneal transplant patients. Therefore, the number of cases reported after vaccination was considered to be within the range of CGR events that would be expected in non-vaccinated individuals.

PRAC acknowledged that awareness and management of CGR, regardless of cause, is part of routine clinical practice.

Comirnaty (BioNTech Manufacturing GmbH)

A PRAC assessment concluded that the available evidence does not support a causal relationship of corneal graft rejection with Comirnaty (see page 2).

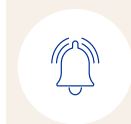
Myocarditis and pericarditis

Update to the product information

In December 2021, PRAC concluded that the risk of myocarditis and pericarditis (inflammatory conditions of the heart) after vaccination with Comirnaty is highest in young males, especially after the second vaccination (see [safety update of December 2021](#)). Overall, there is a very rare risk of myocarditis and pericarditis following vaccination with Comirnaty regardless of dose.

PRAC has continued monitoring this risk and assessed recent data, including a US study² that analysed data from three safety monitoring systems. Based on this new information, PRAC has recommended an update to the EU product information to state that the risk of myocarditis and pericarditis seems lower in children aged 5 to 11 years than in those aged 12 to 17 years. The overall frequency category of myocarditis/pericarditis is already described in the product information as very rare (i.e. occurring in less than 1 in 10,000 persons vaccinated).

The current product information contains the following advice:



Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Vulval ulceration

Assessment started

A very small number of cases of vulval ulceration will be assessed to determine whether they may have been caused by Comirnaty. Vulval ulcerations are usually self-limiting sores on the outer parts of the female genitals. Reported cases concern suspected side effects, i.e. medical events

² Hause AM et al. Safety of COVID-19 vaccination in United States children ages 5 to 11 years. *Pediatrics*. 2022;150: e2022057313.

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

Histiocytic necrotising lymphadenitis

Monitored within routine safety surveillance

A very small number of cases of histiocytic necrotising lymphadenitis (HNL) will be further monitored and assessed within the regular safety surveillance of Comirnaty. HNL is a condition involving swollen lymph nodes, mild fever and night sweats, and is usually transient and self-limiting. 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.



About 663 million doses of Comirnaty, including about 55 million doses in children and adolescents (below 18 years of age), were administered in the EU/EEA from authorisation to 14 August 2022.³

The initial conditional marketing authorisation for Comirnaty in the EU was issued on 21 December 2020. 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 (inactivated, adjuvanted) Valneva (Valneva Austria GmbH)

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

By 14 August 2022, COVID-19 Vaccine (inactivated, adjuvanted) Valneva had not yet been used in the EU/EEA².

The initial 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).

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.

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 14 August 2022.⁴

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.



About 262,000 doses of Nuvaxovid in adults were administered in the EU/EEA from authorisation to 14 August 2022.³

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).

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.

Spikevax (Moderna Biotech Spain, S.L.)

A PRAC assessment concluded that the available evidence does not support a causal relationship of corneal graft rejection with Spikevax (see page 2).

Myocarditis and pericarditis

Update to the product information

In December 2021, PRAC concluded that the risk of myocarditis and pericarditis (inflammatory conditions of the heart) after vaccination with Spikevax is highest in young males, especially after the second vaccination (see [safety update of December 2021](#)). The product information of Spikevax has been updated to reflect that the risk profile for myocarditis and pericarditis seems to be similar after the second and the third dose. The overall frequency category of myocarditis/pericarditis is already described in the product information as very rare (i.e. occurring in less than 1 in 10,000 vaccinated persons).

The current product information contains the following advice:



Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.



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 14 August 2022.⁵

The initial conditional marketing authorisation for Spikevax (previously COVID-19 Vaccine Moderna) in the EU was issued on 06 January 2021. Information on how Spikevax works is provided in the [medicine overview](#) (in all EU/EEA languages). Full information on the vaccine, including all

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.

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, apart from a PRAC assessment concluding that the available evidence does not support a causal relationship of corneal graft rejection with Vaxzevria (see page 2).



About 69 million doses of Vaxzevria in adults were administered in the EU/EEA from authorisation to 14 August 2022.⁶

The initial conditional marketing authorisation for Vaxzevria (previously COVID-19 Vaccine AstraZeneca) in the EU was issued on 29 January 2021. 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 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.

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.

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 29 August 2022, EudraVigilance contained the following:

- Comirnaty: a total of 905,189 cases of suspected side effects spontaneously reported from EU/EEA countries; 8,209 of these reported a fatal outcome^{7,8} (by 14 August 2022, about 663 million doses of Comirnaty had been given to people in the EU/EEA⁹)
- COVID-19 Vaccine (inactivated, adjuvanted) Valneva: no cases of suspected side effects spontaneously reported from EU/EEA countries^{6,7} (by 14 August 2022, the vaccine had not yet been used in the EU/EEA⁸)

⁷ 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).

⁸ 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.

⁹ 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.

- Jcovden: a total of 56,367 cases of suspected side effects spontaneously reported from EU/EEA countries; 333 of these reported a fatal outcome^{10,11} (by 14 August 2022, about 19.4 million doses of Jcovden had been administered to people in the EU/EEA¹²)
- Nuvaxovid: a total of 1,280 cases of suspected side effects spontaneously reported from EU/EEA countries; none of these reported a fatal outcome^{9,10} (by 14 August 2022, about 262,000 doses of Nuvaxovid had been administered to people in the EU/EEA¹¹)
- Spikevax: a total of 247,645 cases of suspected side effects spontaneously reported from EU/EEA countries; 1,127 of these reported a fatal outcome^{9,10} (by 14 August 2022, about 158 million doses of Spikevax had been given to people in the EU/EEA¹¹)
- Vaxzevria: a total of 312,032 cases of suspected side effects spontaneously reported from EU/EEA countries; 1,564 of these reported a fatal outcome^{9,10} (by 14 August 2022, about 69 million doses of Vaxzevria had been given to people in the EU/EEA¹¹).

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.

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

¹⁰ 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).

¹¹ 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.

¹² 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.

plan: [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 5 years), Nuvaxovid (as of 12 years) and Spikevax (as of 6 years).

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

