



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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COVID-19 vaccine safety update

VAXZEVRIA

AstraZeneca AB

The safety of Vaxzevria 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 11 August 2021.

Main outcomes from PRAC's latest safety assessment

The product information will be updated with Guillain-Barré syndrome (GBS) as a side effect of Vaxzevria.

Pain in legs and arms or stomach and influenza-like symptoms have also been included in the product information as side effects.

¹ Correction was made on page 6 reflecting MHRAs assessment on case reports of menstrual disorders.

The safety updates are published regularly at [COVID-19 vaccines: authorised](#). All published safety updates for Vaxzevria are available at [Vaxzevria: safety updates](#).

Since its marketing authorisation in the European Union (EU) on 29 January 2021 until 2 September 2021, more than 68.4 million doses of Vaxzevria have been administered in the EU/EEA².



1. Updates on safety assessments for Vaxzevria

PRAC assessed new safety data, including the latest Monthly Summary Safety Report (MSSR)³ from the marketing authorisation holder and data reported by patients and healthcare professionals to EudraVigilance (see section 2), during its meeting held 30 August to 2 September 2021.

Guillain-Barré syndrome

Update to the Vaxzevria product information

A warning to raise awareness of cases of Guillain-Barré syndrome (GBS) reported following vaccination was included in the product information of Vaxzevria following PRAC in July 2021⁴.

GBS is a serious nerve inflammation, which may cause temporary loss of feeling and movement (paralysis) and difficulty breathing.

PRAC has been keeping GBS under close monitoring and in September 2021 assessed additional data requested from the marketing authorisation holder and the results from a scientific literature review. A total of 833 cases of GBS had been reported with Vaxzevria worldwide by 31 July 2021, while around 592 million doses of Vaxzevria had been given to people worldwide by 25 July 2021. Reported cases concern suspected side

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.

³ Monthly Summary Safety Reports, also referred to as pandemic summary safety reports, will be compiled by the marketing authorisation holders to support timely and continuous benefit-risk evaluations for COVID-19 vaccines used during the pandemic. These reports complement the submission of [Periodic Safety Update Reports](#) (PSURs).

⁴ See [safety update for Vaxzevria of 14 July 2021](#)

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 the assessment of these data and taking into account neurological expert advice, PRAC concluded that a causal relationship between Vaxzevria and GBS is considered at least a reasonable possibility and that GBS should therefore be added to the product information as a side effect of Vaxzevria. The frequency category allocated is 'very rare' (i.e. occurring in less than 1 in 10,000 persons), which is the category of the lowest frequency foreseen in EU product information. Further, PRAC recommended to update the existing warning in the package leaflet with the following advice:

Patients are asked to talk to their healthcare professionals before they are given Vaxzevria if they previously had GBS after being given Vaxzevria.

Reminder: People should seek immediate medical attention if they develop weakness and paralysis in the extremities that can progress to the chest and face.

Capillary leak syndrome (CLS)

No further update to the Vaxzevria product information at present

In June 2021, capillary leak syndrome (CLS) was identified as a side effect of Vaxzevria and the product information was updated.

Capillary leak syndrome is a very rare, serious condition that causes fluid leakage from small blood vessels (capillaries) and is potentially fatal⁵.

In September 2021, PRAC further assessed hypotheses of a possible mechanism of action for the development of CLS following vaccination. Having assessed the available data, including from a review of the scientific literature, PRAC concluded that no definitive mechanism could be identified. While this assessment procedure was closed, data which may emerge in the future will be monitored and assessed as part of the MSSR and PSUR processes for Vaxzevria.

Reminder: People who have a previous diagnosis of CLS must not be vaccinated with Vaxzevria (contraindication) and people should seek immediate medical attention if they experience rapid swelling of the arms and legs, sudden weight gain and feeling faint (low blood pressure) in the days following vaccination with Vaxzevria.

Thrombosis with thrombocytopenia syndrome (TTS)

Update to the Vaxzevria product information

⁵ See [safety update for Vaxzevria of 18 June 2021](#)

In May 2021, the product information of Vaxzevria was updated with regard to the very rare risk of thrombosis (formation of blood clots in the blood vessels) with thrombocytopenia (low blood platelets) syndrome (TTS)⁶.

Data on TTS are kept under close monitoring for further characterisation of risk factors⁷. In September 2021, PRAC concluded to further update the product information by removing the current statement that reported TSS cases occurred mostly in women under 60 years of age, since the age and sex imbalance seemed smaller than previously observed.

This conclusion is based on the latest analyses of spontaneously reported TTS cases which include 43% of the cases in males and 37% in vaccinated persons older than 60 years, and on data analyses in the scientific literature⁸ which did not identify a large difference of TTS cases by sex. A total of 1,503 cases had been reported worldwide as of 31 July 2021, while around 592 million doses of Vaxzevria had been given to people worldwide by 25 July 2021. 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.

Close monitoring and risk characterisation of TTS will continue as part of the MSSR and PSUR processes for Vaxzevria.

Reminder: People should seek immediate medical attention if they experience severe or persistent headache, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, unusual skin bruising or pinpoint round spots beyond the site of vaccination within three weeks of vaccination, as these could be signs of TTS.

Cerebral venous sinus thrombosis (CVST) without thrombocytopenia

Assessment ongoing

In the context of its regular reviews of the MSSRs, PRAC is assessing cases of cerebral venous sinus thrombosis (CVST, a rare form of stroke where a blood clot forms in the brain's venous sinuses) without thrombocytopenia (low levels of blood platelets) reported after vaccination with Vaxzevria. PRAC has requested the marketing authorisation holder to provide further data in the next MSSR.

Multisystem inflammatory syndrome (MIS)

⁶ See [safety update for Vaxzevria of 11 May 2021](#)

⁷ See [Article 5\(3\) procedure for Vaxzevria in April 2021](#)

⁸ Arepally GM, Ortel TL. Vaccine-induced immune thrombotic thrombocytopenia: what we know and do not know. *Blood*. 2021; 138: 293-298. Epub 2021 Jun 1. and Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, Rampotas A, Ambler G, Makris M. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. *N Engl J Med*. 2021 Aug 11 (Epub ahead of print).

Assessment ongoing

PRAC is assessing whether there is a risk of multisystem inflammatory syndrome (MIS) with COVID-19 vaccines following a report of MIS with Comirnaty, another COVID-19 vaccine, in Denmark. Some cases of MIS after administering Comirnaty or other COVID-19 vaccines were reported in adults and/or from outside EU/EEA. 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.

MIS is a serious inflammatory condition affecting many parts of the body and symptoms can include tiredness, persistent severe fever, diarrhoea, vomiting, stomach pain, headache, chest pain and difficulty breathing.

MIS is rare and its incidence rate before the COVID-19 pandemic estimated from 5 European countries was around 2 to 6 cases per 100,000 per year in children and adolescents below 20 years of age and less than 2 cases per 100,000 per year in adults aged 20 years or above [data from observational studies coordinated by EMA (see section 2)]⁹. MIS has also been reported following COVID-19 disease. The Danish patient, however, had no history of COVID-19.

As of 19 August 2021, no cases were reported as MIS in a child after vaccination with Vaxzevria in the EEA/EU to EudraVigilance (for information on EudraVigilance, see section 2).

PRAC will now assess the available data on MIS to determine whether the condition can be caused by COVID-19 vaccines and recommend whether any changes to the product information are needed.

PRAC encourages all healthcare professionals to report any cases of MIS and other adverse events in people who have had these vaccines (for advice on reporting, see section 2).

At this stage, there is no change to the current EU recommendations for the use of COVID-19 vaccines.

EMA and national authorities will provide further updates as necessary¹⁰.

Menstrual disorders

No evidence for causal relationship with Vaxzevria

PRAC assessed reported cases of menstrual disorders occurring after vaccination with Vaxzevria and a review of the scientific literature, including non-clinical studies. Until 31 July 2021, a total of 12,410 cases had been reported worldwide, of which 663 (5.3%) were medically confirmed as menstrual disorder (511 in pre-menopausal and 89 in post-

⁹ See [European Network of Centres for Pharmacoepidemiology and Pharmacovigilance \(ENCePP\)](#)

¹⁰ See [Meeting Highlights from the Pharmacovigilance Risk Assessment Committee \(PRAC\) 30 August - 2 September 2021](#)

menopausal women; 242 medically confirmed events were classified as serious). These reports emerged from worldwide Vaxzevria use of around 592 million administered doses by 25 July 2021. 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 - conducted with gynaecological expert advice - included analysing the type of symptoms, their time to onset, duration and outcome as well as any concomitant treatment and medical history; no common pattern could be identified. Also, no potential mechanism of action for the vaccine causing symptoms of menstrual disorder could be identified.

PRAC also considered the assessment of the Medicines & Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) of August 2021, 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 Vaxzevria¹¹.

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

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.

Women experiencing unexpected vaginal bleeding (e.g. in postmenopausal women) or who are concerned about prolonged or severe menstrual disturbances may want to seek medical advice.

Other events: Pain and influenza-like symptoms

Update to the Vaxzevria product information

In the context of an ongoing review of clinical trial data, pain in the extremity (legs and arms), abdominal (stomach) pain and influenza-like symptoms (such as high temperature, sore throat, runny nose, cough and chills) were added as side effects to the product information of Vaxzevria, following the outcome of the [Committee for Medicinal Products for Human Use](#) (CHMP) of June 2021¹². Pain in the extremity and influenza-like symptoms occur with a frequency of common (i.e. occurring in less than 1

¹¹ For the latest UK data, see [Coronavirus vaccine – weekly summary of Yellow Card reporting](#)

¹² See [minutes of the Committee for Medicinal Products for Human Use meeting in June 2021](#)

in 10 persons) and abdominal pain with a frequency of uncommon (i.e. occurring in less than 1 in 100 persons).

2. How safety is monitored

As for all COVID-19 vaccines, relevant new information emerging on Vaxzevria 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).

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, 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 VACCINE ASTRAZENECA (CHADOX1 NCOV-19)” to see all suspected side effect cases reported for Vaxzevria.

As of 2 September 2021, a total of 184,679 cases of suspected side effects with Vaxzevria were spontaneously reported to EudraVigilance from EU/EEA countries; 1,149 of these reported a fatal outcome^{13,14}. By the same date, more than 68.4 million doses of Vaxzevria had been given to people in the EU/EEA¹⁵.

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

¹³ 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).

¹⁴ 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.

¹⁵ 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.

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 Vaxzevria will continue to provide results from the main clinical trials, which are ongoing. 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 Vaxzevria, see the [risk management plan](#).

A [paediatric investigation plan](#) (PIP) for Vaxzevria is in place. This describes how the company will collect data on the vaccine's efficacy and safety for its potential 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 Vaxzevria

Vaxzevria (previously COVID-19 Vaccine AstraZeneca) is a vaccine that was authorised in the EU on 29 January 2021 for use in people aged 18 years and older to prevent COVID-19 when infected with the coronavirus SARS-CoV-2. COVID-19 is a potentially severe disease that may result in death.

Vaxzevria contains an adenovirus that has been modified to carry molecules of DNA, which the body uses to temporarily produce the SARS-CoV-2 spike protein. The spike protein does not cause COVID-19. The adenovirus cannot reproduce and does not cause viral disease.

Before Vaxzevria 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 12,000 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 Vaxzevria are usually mild or moderate and get better within a few days after vaccination.

More information on how Vaxzevria 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.

Medicinal product no longer authorised

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