EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 June 2021

COVID-19 vaccine safety update

VAXZEVRIA

AstraZeneca AB

People who have previously had capillary leak syndrome must not receive Vaxzevria.

Capillary leak syndrome may also occur as a side effect of Vaxzevria.

The product information will be updated.

Vaxzevria is effective in preventing COVID-19.

This safety update follows the last update of 21 May 2021.

Safety updates provide information about the assessments of emerging worldwide safety data since marketing authorisation for COVID-19 vaccines. Safety assessments are carried out primarily by EMA's Pharmacovigilance Risk Assessment Committee (PRAC). 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 10 June 2021, almost 46 million doses of Vaxzevria have been administered in the EU/EEA[1].

1. Updates on safety of Vaxzevria

Based on new safety data, including the latest Monthly Summary Safety Report (MSSR)[2] from the marketing authorisation holder and data reported by patients and healthcare professionals to EudraVigilance (see section 3), PRAC assessed the following at its meeting held 7 to 10 June 2021:

Capillary leak syndrome

PRAC identified capillary leak syndrome as a side effect of Vaxzevria and also concluded that people who have previously had capillary leak syndrome must not be vaccinated with Vaxzevria (contraindication). The product information will be updated accordingly, together with a warning to raise awareness among healthcare professionals and patients of this risk. Patients with an acute episode of capillary leak syndrome following vaccination require prompt treatment and may require intensive supportive therapy and continuous specialist monitoring.

Capillary leak syndrome is a very 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 conclusion is based on an in-depth review of six cases of capillary leak syndrome in people who had received Vaxzevria (a total of 14 reports of capillary leak syndrome to EudraVigilance were reviewed initially, out of which six had sufficient information for further assessment and were considered to be cases of capillary leak syndrome). Most of the cases occurred in women and within four days of vaccination. Three of those affected had a history of capillary leak syndrome, and one of them subsequently died. These cases were reported from the EU/EEA and the United Kingdom, where a total of more than 78 million doses of Vaxzevria had been administered as of 27 May 2021[3]. The product information will

[1] The European Centre for Disease Prevention and Control (ECDC) collects these data from EU Member States as well as from the additional countries of the European Economic Area (EEA) Norway, Iceland and Liechtenstein.

[2] 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).

[3] For the latest UK data, see Coronavirus vaccine – weekly summary of Yellow Card reporting

list capillary leak syndrome as a side effect of unknown frequency, because it is generally difficult to robustly estimate side effect frequencies from spontaneously reported cases of suspected side effects.

A direct healthcare professional communication (DHPC) to raise awareness will be sent in due course to healthcare professionals prescribing, dispensing or administering the vaccine. The DHPC will also be published on the EMA website.

People who have been vaccinated with Vaxzevria should seek immediate medical assistance if they experience rapid swelling of the arms and legs or sudden weight gain in the days following vaccination. These symptoms may be associated with feeling faint (due to low blood pressure).

PRAC will continue to monitor for cases of capillary leak syndrome and will take further actions if necessary. PRAC also asked the marketing authorisation holder for further information about a possible mechanism for the development of capillary leak syndrome following vaccination[4].

Guillain-Barré syndrome (GBS)

PRAC continued assessing cases of Guillain-Barré syndrome (GBS) reported after vaccination with Vaxzevria.

GBS is an immune system disorder that causes nerve inflammation and can result in pain, numbness, muscle weakness and difficulty walking.

A total of 156 cases of GBS had been reported from the EU/EEA to EudraVigilance with Vaxzevria by the end of May 2021, at which time around 40 million doses of Vaxzevria had been administered in the 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.

PRAC is collecting further data in order to conclude its assessment. This includes data requested from the marketing authorisation holder, in particular refined analyses taking into account GBS frequencies in the general (non-vaccinated) population by age group and sex, an in-depth review of all data from pre-clinical studies, clinical trials, vaccination campaigns and the scientific literature, and investigations into the biological plausibility of a possible causal relationship between GBS and Vaxzevria.

PRAC encourages all healthcare professionals and patients to report any cases of GBS and other adverse events in people after vaccination.

[4] See EMA public health communication on capillary leak syndrome with Vaxzevria of 11 June 2021

Myocarditis and pericarditis

PRAC is continuing its assessment of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the membrane around the heart) reported in a small number of people following vaccination with COVID-19 vaccines. This assessment follows case reports of myocarditis/pericarditis after vaccination with Comirnaty, another COVID-19 vaccine, as presented in the Comirnaty safety update of May 2021[5].

For Vaxzevria, 38 cases of myocarditis and 47 cases of pericarditis had been reported from the EU/EEA to EudraVigilance by the end of May 2021, at which time around 40 million doses of Vaxzevria had been administered in the EU/EEA. Cases reported to EudraVigilance 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.

Currently, further analysis is needed to conclude whether there is a causal relationship between myocarditis/pericarditis and COVID-19 vaccines, and PRAC has requested additional data from the companies marketing the vaccines.

PRAC encourages all healthcare professionals and patients to report any cases of myocarditis or pericarditis and other adverse events occurring in people after vaccination.

Myocarditis and pericarditis are inflammatory diseases of the heart that can occur following infections or immune diseases. Depending on the data source, the incidence estimates for myocarditis and pericarditis in the general (unvaccinated) EU/EEA population prior to the COVID-19 pandemic range from 1 to 10 in 100,000 people per year. Symptoms of myocarditis and pericarditis can vary but often include shortness of breath, a forceful heartbeat that may be irregular and chest pain. The conditions usually improve on their own or with treatment. Patients who have such symptoms should consult their doctor[6].

Embolic and thrombotic events with a focus on thrombosis with thrombocytopenia syndrome (TTS)

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)[7]. In June 2021, PRAC considered the current data consistent with the aspects known so far for TTS.

TTS requires rapid identification and urgent clinical management. On 7 June 2021, EMA issued a communication to raise awareness of clinical care recommendations to manage suspected TTS. The recommendations

[5] See safety update for Comirnaty of 11 May 2021

[6] See EMA public health communication on myocarditis and pericarditis with COVID-19 vaccines of 11 June 2021

[7] See safety update for COVID-19 Vaccine Janssen of 11 May 2021

from the International Society on Thrombosis and Haemostasis (ISTH)[8] and learned societies in EU Member States were specifically highlighted[9].

PRAC will continue to closely monitor TTS.

Acute disseminated encephalomyelitis (ADEM) and encephalitis

PRAC has started an assessment of cases of acute disseminated encephalomyelitis (ADEM) and encephalitis reported as suspected side effects of Vaxzevria to EudraVigilance.

ADEM is an autoimmune disease characterised by sudden, widespread inflammation in the brain and spinal cord; encephalitis is inflammation of the brain.

Ten cases of ADEM and 33 cases of encephalitis had been reported from the EU/EEA to EudraVigilance with Vaxzevria by the end of May 2021, at which time around 40 million doses of Vaxzevria had been administered in the EU/EEA. Cases reported to EudraVigilance 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.

At present a causal relationship of these conditions with Vaxzevria has not been confirmed, and further data will be compiled and assessed. This includes a cumulative review of all cases of ADEM and encephalitis, including an observed-versus-expected analysis with stratification by age and taking into account different possible risk periods, and an in-depth discussion, classification and causality assessment of each case requested from the marketing authorisation holder.

PRAC encourages all healthcare professionals and patients to report any cases of ADEM or encephalitis and other adverse events occurring after vaccination.

Pain and influenza-like symptoms

PRAC revised the risk management plan in the context of an ongoing review of clinical trial data by the Committee for Medicinal Products for Human Use (CHMP) to add pain in the extremity (limb), abdominal (belly) pain and influenza-like symptoms (such as high temperature, sore throat, runny nose, cough and chills) to the product information of Vaxzevria as side effects.

[8] See International Society of Thrombosis and Haemostasis

[9] See EMA public health communication on clinical care recommendations to manage suspected thrombosis with thrombocytopenia syndrome of 7 June 2021

2. 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 have 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.

3. 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).

Collecting case reports of suspected side effects

The EU regulatory network continuously monitors reports of suspected side effects observed in vaccinated individuals. These case reports are collected and recorded in EudraVigilance, a system operated by EMA for managing and analysing information on suspected side effects of medicines.

Vaccinated individuals and healthcare professionals should report suspected side effects via the national reporting systems, which also contribute to EudraVigilance. For more information, see Reporting suspected side effects. Information on how to report in your Member State

is available in the package leaflet and via the list of national competent authorities.

You may visit EudraVigilance – European database of suspected drug reaction reports in all EU/EEA languages and search for "COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19)" to see all suspected side effects reported for Vaxzevria in the EU/EEA. Please note that these reports describe suspected side effects in individuals, i.e. these events may not necessarily have been caused by, or be otherwise related to, the vaccine.

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.

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