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COVID-19 Vaccines Pharmacovigilance Update

COVID-19 vaccines are being used extensively across the EU/EEA as part of mass vaccination campaigns, with the European Centre for Disease Prevention and Control (ECDC) estimating that, as of 29 July 2021, over 455 million doses have been administered, with over 5.6 million of those in Ireland. To date, the European Medicines Agency (EMA) has granted conditional marketing authorisation for four COVID-19 vaccines*, with additional vaccines being evaluated through ongoing rolling reviews. More information on authorised COVID-19 vaccines, as well as those under evaluation in the EU may be found on the [EMA website](#).

In February 2021, the HPRA published a [special edition](#) of the Drug Safety Newsletter (DSN), describing the intensified pharmacovigilance planned for COVID-19 vaccines, and highlighting the importance of reporting suspected adverse reactions. Through ongoing monitoring of emerging data, including from use in mass vaccination campaigns, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), in which the HPRA participates, has reaffirmed that the benefits of authorised vaccines outweigh the risks in preventing COVID-19 illness and related complications, including death and hospitalisation.

In this edition, the recommendations and advice issued by the PRAC to healthcare professionals, concerning a small number of very rare but important adverse reactions associated with COVID-19 vaccines, are highlighted.

To date, the HPRA has published nine COVID-19 safety update reports, which provide an overview of national reporting experience. These updates, as well as previous DSNs and direct healthcare professional communications (DHPCs) on specific topics, are available on the HPRA's dedicated [COVID-19 Vaccine Safety Updates and Communications](#) webpage.

The HPRA continues to encourage healthcare professionals to report suspected adverse reactions via www.hpra.ie/report, in particular those that are serious or have occurred in special populations. Reporting adverse reactions to the HPRA supports continuous monitoring of safe and effective use of COVID-19 vaccines.

* Currently authorised COVID-19 Vaccines include mRNA vaccines - [Comirnaty®](#) and [Spikevax®](#) (previously COVID-19 Vaccine Moderna), and adenoviral vector vaccines - [Vaxzevria®](#) (previously COVID-19 Vaccine AstraZeneca) and [COVID-19 Vaccine Janssen®](#). Further information is available on www.hpra.ie and www.ema.europa.eu

Myocarditis and pericarditis – Comirnaty® and Spikevax®

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (the PRAC) completed a review of very rare cases of myocarditis and pericarditis occurring in people following vaccination with mRNA vaccines, Comirnaty® and Spikevax® (previously COVID-19 Vaccine Moderna), and concluded that a causal association is at least a reasonable possibility. Accordingly, the product information has been revised to include myocarditis and pericarditis as possible adverse reactions, together with advice for healthcare professionals on this risk.

Myocarditis and pericarditis are inflammatory diseases of the heart that can typically occur following an infection or due to autoimmune disease. Symptoms can vary but often include breathlessness, palpitations, and chest pain. People with myocarditis or pericarditis may require specialist treatment.

The PRAC review considered all available evidence, including an in-depth evaluation of very rare cases reported in the EU/EEA. As of 31 May 2021, 145 cases of myocarditis were reported among people who received Comirnaty® and 19 cases among people who received Spikevax®. The PRAC also reviewed reports of 138 cases of pericarditis following the use of Comirnaty® and 19 cases following the use of Spikevax®. Around 177 million doses of Comirnaty® and 20 million doses of Spikevax® had been given in the EU/EEA at that time.

The cases of myocarditis and pericarditis reviewed have primarily occurred within 14 days after vaccination, more often in younger men and after the second dose. Five cases that occurred in the EU/EEA were fatal. The individuals were either of advanced age or had concomitant diseases. The available data suggest that the course of myocarditis and pericarditis following vaccination is similar to the course of myocarditis and pericarditis in general.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for the mRNA vaccines, [Comirnaty®](#) and [Spikevax®](#), has been updated to include warnings and precautions for myocarditis and pericarditis and to list these as possible adverse reactions with frequency 'not known'.

The relevant market authorisation holders (MAHs), in agreement with the HPRA, have issued a [Direct Healthcare Professional Communication \(DHPC\)](#), which includes advice to healthcare professionals.

The PRAC will continue to monitor emerging data regarding myocarditis and pericarditis for all COVID-19 vaccines and will take further actions as necessary.

Advice to Healthcare Professionals

- Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in people who have received Comirnaty® or Spikevax®.
- Those vaccinated should be instructed to seek immediate medical attention if they experience (acute or persisting) chest pain, palpitations or shortness of breath.
- People with myocarditis or pericarditis may require specialist treatment. Healthcare professionals should consult the applicable clinical guidance and/or consult specialists (e.g. cardiologists) to diagnose and treat these conditions.

Key Message

Cases of myocarditis and pericarditis have been reported very rarely following vaccination with the COVID-19 mRNA vaccines Comirnaty® and Spikevax®.

The cases primarily occurred within 14 days after vaccination, more often in younger men and after the second dose.

Available data suggest that the course of myocarditis and pericarditis following vaccination is similar to the course of myocarditis and pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.

Healthcare professionals should advise vaccinated individuals to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations.

Healthcare professionals are encouraged to report suspected adverse reactions, including adverse events of special interest, such as myocarditis or pericarditis, to the HPRA via www.hpra.ie/report.

Thrombosis with thrombocytopenia syndrome (TTS) – Vaxzevria® and COVID-19 Vaccine Janssen®

Vaxzevria® (previously COVID-19 Vaccine AstraZeneca) and COVID-19 Vaccine Janssen® are adenoviral vector vaccines which received conditional marketing authorisations in the EU in January and March 2021, respectively. Use of both vaccines has been associated with a very rare risk of developing a condition known as thrombosis with thrombocytopenia syndrome (TTS).

In March 2021, the EMA's Pharmacovigilance Risk Assessment Committee (the PRAC) initiated a review of embolic and thromboembolic events following vaccination with Vaxzevria®. The review involved evaluation of data from different sources including spontaneous reports from the EMA database of suspected adverse reactions (EudraVigilance), individual cases, "observed versus expected" analyses, available literature as well as input from an *ad hoc* expert group. Some of the cases under review were severe and presented as venous thrombosis in unusual sites, such as cerebral venous sinus thrombosis and splanchnic vein thrombosis, as well as arterial thrombosis, often concomitant with thrombocytopenia and in some cases accompanied by bleeding. Other cases involved thrombosis in more typical sites, including deep vein thrombosis (DVT) or pulmonary embolism (PE). The majority occurred within two to three weeks of the first dose of Vaxzevria®, mainly in women under 60 years of age, possibly reflecting exposure patterns to Vaxzevria® in the EU/EEA at that time. In a number of cases, there was a fatal outcome.

The product information for [Vaxzevria®](#) was updated at that time with a warning that thrombosis together with thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination. Healthcare professionals were advised that individuals diagnosed with thrombocytopenia within three weeks after vaccination with Vaxzevria®, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia.

In April 2021, the PRAC concluded that a causal relationship between Vaxzevria and TTS was at least a reasonable possibility, with TTS added to the product information as a possible adverse reaction with a frequency of 'very rare'. A contraindication in individuals who have experienced TTS following previous vaccination with Vaxzevria® was subsequently added in May 2021.

A further analysis and stratification of data was performed by the EMA in April 2021 to put the very rare cases of TTS associated with Vaxzevria® in the context of the benefits of vaccination. That analyses conducted show that the benefits of vaccination improve with increasing age and increasing infection rates¹.

In April 2021, following a review of US data and prior to the commencement of the use of the vaccine in immunisation programmes across the EU/EEA, the PRAC concluded that a warning about TTS should also be included in the product information for COVID-19 Vaccine Janssen®. TTS was listed as a possible adverse reaction of the vaccine with a frequency of 'very rare'. The product information was subsequently further updated in May 2021 to include current advice on the signs and symptoms, detection, diagnosis and treatment of TTS.

Interim case definitions for TTS focus on cases that have both thrombocytopenia and thrombosis². In several of the reported cases with concomitant thrombosis and thrombocytopenia, testing for anti-platelet factor 4 (PF4) antibodies was positive or strongly positive. Extensive work-up for other potential mechanisms that could cause thrombosis and/or thrombocytopenia has been provided for a minority of these cases; however, no other abnormalities have been found that are considered to explain the observed events. The exact pathophysiological mechanism for the occurrence of these thrombotic events is not defined yet; with the understanding of the role of PF4 antibodies still evolving.

Epidemiology and risk factors for TTS are yet to be fully characterised. A number of studies are being put in place to identify the exact pathophysiological mechanism for the occurrence of these thrombotic events and define the precise magnitude of the risk. Summaries of national cases of suspected TTS are provided in the HPRAs Safety Updates on COVID-19 Vaccines, the most recent of which was published on [15 July 2021](#). Information on reporting rates of cases of TTS based on post marketing experience in the EU/EEA and in the UK have been published by the [EMA](#) and [MHRA](#), respectively.

The very rare risk of TTS with these vaccines was highlighted in [Direct Healthcare Professional Communications \(DHPCs\) and Issues 102 and 103 of the HPRAs Drug Safety Newsletter](#). In June 2021, the EMA published a [statement](#) to raise awareness amongst healthcare professionals of TTS clinical care recommendations issued by learned societies. The Irish Haematology Society Coagulation Special Interest Group have also published [Guidance on the diagnosis and management of thrombocytopenia and thrombosis](#). A summary of current regulatory advice is outlined in the section 'Advice to Healthcare Professionals' below.

The PRAC will continue to monitor emerging evidence regarding TTS and will take further actions as necessary.

Advice to Healthcare Professionals

- Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia.
- Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, leg pain or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, blurred vision, confusion or seizures after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.
- Individuals presenting with thrombocytopenia within three weeks after vaccination should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia.
- TTS requires specialised clinical management. Healthcare professionals should consult the applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat patients presenting with thrombocytopenia and/or thrombosis following vaccination with either COVID-19 Vaccine Janssen® or Vaxzevria®. Guidance on diagnosis and management of thrombocytopenia and thrombosis, devised by the Irish Haematology Society Coagulation Special Interest Group, is available on the [HSE website section on COVID-19 Vaccine Information for Health Professionals](#) under 'Clinical Information'.

Key Message

A combination of thrombosis and thrombocytopenia (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with adenoviral vector vaccines Vaxzevria® and COVID-19 Vaccine Janssen®. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first three weeks following vaccination.

Individuals diagnosed with thrombocytopenia within three weeks after vaccination with Vaxzevria® or COVID-19 Vaccine Janssen® should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia.

TTS requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g. haematologists, specialists in coagulation) to diagnose and treat this condition.

The second dose of Vaxzevria® is contraindicated for people who have experienced TTS following previous vaccination with Vaxzevria®.

Healthcare professionals are encouraged to report suspected adverse reactions, including adverse events of special interest, such as TTS, to the HPRa via www.hpra.ie/report.

References

1. European medicines Agency: Assessment report EMA/239822/2021 https://www.ema.europa.eu/en/documents/referral/use-vaxzevria-prevent-covid-19-article-53-procedure-assessment-report_en.pdf (Accessed 20 July 2021)
2. Updated Proposed Brighton Collaboration process for developing a standard case definition for study of new clinical syndrome X, as applied to Thrombosis with Thrombocytopenia Syndrome (TTS). <https://brightoncollaboration.us/wp-content/uploads/2021/05/TTS-Interim-Case-Definition-v10.16.3-May-23-2021.pdf>

Capillary Leak Syndrome – Vaxzevria® and COVID-19 Vaccine Janssen®

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (the PRAC) recommended updates to the product information for Vaxzevria® (previously COVID-19 Vaccine AstraZeneca) and COVID-19 Vaccine Janssen®, to reflect current scientific knowledge and advice on capillary leak syndrome (CLS).

CLS is a rare disorder characterised by a dysfunctional inflammatory response, endothelial dysfunction, and extravasation of fluid from the vascular space to the interstitial space leading to shock, haemoconcentration, hypoalbuminaemia and potentially consequent organ failure. Patients may present with a rapid swelling of the arms and legs, sudden weight gain and feel faint due to low blood pressure. CLS occurs rarely in the general population with fewer than 500 cases described worldwide in the literature¹, however, it is likely that estimates are lower than the true event rates. Some cases of systemic CLS reported in the literature have been triggered by COVID-19 infection.

The updates to product information follow an in-depth review by the PRAC of six reports of CLS in people vaccinated with Vaxzevria®, mostly within four days of vaccination. A history of CLS was apparent in some of the cases, with a fatal outcome reported in one case. The PRAC also reviewed three cases of CLS in people who had received COVID-19 Vaccine Janssen®, and which occurred within two days of vaccination. One of those affected had a history of CLS and two subsequently died. Overall, the reporting rate of CLS is estimated to be one case per 5 million doses of Vaxzevria®, and one case per 6 million doses of COVID-19 Vaccine Janssen®.

Vaxzevria® and COVID-19 Vaccine Janssen® are both contraindicated in any individual who has previously experienced episodes of CLS. Product information for both vaccines has been updated to include CLS as a possible adverse reaction with a frequency of 'not known'.

Direct Healthcare Professional Communications (DHPCs) regarding CLS in association with Vaxzevria® and COVID-19 Vaccine Janssen® were circulated in June and July 2021, respectively. The PRAC will continue to monitor emerging data regarding CLS and will take further actions as necessary.

Advice to Healthcare Professionals

- Vaxzevria® and COVID-19 Vaccine Janssen® are contraindicated in individuals who have previously experienced episodes of CLS.
- Healthcare professionals should be aware of the signs and symptoms of CLS. Patients with an acute episode of CLS following vaccination require prompt treatment and may require continuous specialist monitoring and intensive supportive therapy.
- Healthcare professionals should advise patients receiving these vaccines that they must seek medical attention immediately if they experience swelling of the arms and legs or have sudden weight gain in the days after vaccination, which may be associated with feeling faint (due to low blood pressure).

Key Message

Very rare cases of capillary leak syndrome (CLS) have been reported in the first days after vaccination with Vaxzevria® and COVID-19 Vaccine Janssen®, in some cases with a fatal outcome. A history of CLS has been reported in some cases.

Vaxzevria® and COVID-19 Vaccine Janssen® are contraindicated in individuals who have previously experienced episodes of CLS.

CLS is characterised by acute episodes of oedema mainly affecting the limbs, hypotension, haemoconcentration and hypoalbuminaemia. Patients with an acute episode of CLS following vaccination require prompt recognition and treatment. Intensive supportive therapy is usually warranted.

Direct Healthcare Professional Communications (DHPCs) regarding CLS in association with Vaxzevria® and COVID-19 Vaccine Janssen® were circulated in June and July 2021, respectively.

Healthcare professionals are encouraged to report suspected adverse reactions, including adverse events of special interest, such as CLS, to the HPRA via www.hpra.ie/report.

References

1. National Organization for Rare Disorders (2021) Systemic Capillary Leak Syndrome. Available at: <https://rarediseases.org/rare-diseases/systemic-capillary-leak-syndrome/> (Accessed 6 July 2021)

Guillain-Barré Syndrome (GBS) – Vaxzevria® and COVID-19 Vaccine Janssen®

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (the PRAC), has recommended updates to product information for Vaxzevria® (previously COVID-19 Vaccine AstraZeneca) and COVID-19 Vaccine Janssen® to reflect current scientific knowledge on Guillain-Barré syndrome (GBS).

The update follows a review of the available evidence, including very rare reports of GBS occurring following vaccination. For Vaxzevria®, a total of 227 cases of GBS had been reported from the EU/EEA by 27 June 2021, while around 50 million doses had been given. In relation to COVID-19 Vaccine Janssen®, the PRAC assessment took account of 108 cases of GBS reported worldwide as of 30 June 2021, when over 20 million people had received the vaccine. Among these reports, there was one fatal outcome.

Although cases of GBS after Vaxzevria® and COVID-19 Vaccine Janssen® have been reported very rarely, in view of the seriousness of this condition, the PRAC recommended a warning is included in product information, to raise awareness amongst healthcare professionals, and to allow for early diagnosis, supportive care and treatment. Those vaccinated are advised to seek immediate medical attention if they develop signs and symptoms suggestive of GBS.

The PRAC will continue to monitor data regarding GBS and will take further action as necessary.

Advice to Healthcare Professionals

- Cases of GBS have been reported very rarely following vaccination with COVID-19 Vaccine Janssen® and Vaxzevria®.
- Healthcare professionals should be alert to signs and symptoms of GBS to ensure correct diagnosis, to initiate adequate supportive care and treatment and to rule out other causes.
- Healthcare professionals should advise people receiving COVID-19 Vaccine Janssen® or Vaxzevria® to seek immediate medical attention if they develop symptoms suggestive of GBS, such as weakness in the extremities that can progress to the chest and face.

Key Message

Very rare cases of Guillain-Barré syndrome (GBS) have been reported in people that have received Vaxzevria® and COVID-19 Vaccine Janssen®.

The product information for COVID-19 Vaccine Janssen® and Vaxzevria® includes a warning to raise awareness amongst healthcare professionals and people taking the vaccine, and to allow for early diagnosis, supportive care and treatment.

Healthcare professionals are encouraged to report suspected adverse reactions, including adverse events of special interest, such as Guillain-Barré syndrome, to the HPRA via www.hpra.ie/report.

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
COVID-19 Vaccine Janssen	Contraindication in individuals with previous capillary leak syndrome and update on TTS
Comirnaty and Spikevax	Risk of myocarditis and pericarditis
Xeljanz (tofacitinib)	Increased risk of major adverse cardiovascular events and malignancies with use of tofacitinib relative to TNF-alpha inhibitors
Vaxzevria (formerly COVID-19 AstraZeneca)	Contraindication in individuals with previous capillary leak syndrome
Vaxzevria (formerly COVID-19 AstraZeneca)	Risk of thrombosis in combination with thrombocytopenia (updated information)
COVID-19 Vaccine Janssen	Link between the vaccine and the occurrence of thrombosis in combination with thrombocytopenia
Eylea (aflibercept)	Higher risk of intraocular pressure increase with the pre-filled syringe
Vaxzevria (formerly COVID-19 AstraZeneca)	Link between the vaccine and the occurrence of thrombosis in combination with thrombocytopenia
Tecentriq (atezolizumab)	Risk of severe cutaneous adverse reactions (SCARs)
COVID-19 Vaccine AstraZeneca (now called Vaxzevria)	Risk of thrombocytopenia and coagulation disorders
Zolgensma (onasemnogene abeparvovec)	Risk of thrombotic microangiopathy
Esmya (ulipristol acetate)	Indications for uterine fibroids restricted due to concerns of severe liver injury
Lynparza (Olaparib)	Risk of medication errors with new pharmaceutical form
Gilenya (fingolimod)	Updated recommendations to minimize the risk of drug-induced liver injury (DILI)
Tecfidera (dimethyl fumarate)	Updated recommendations for PML in the setting of mild lymphopenia
Trisenox (arsenic trioxide)	Risk of medication errors due to the introduction of 2mg/ml concentration
Esbriet (pirfenidone)	New recommendations to prevent drug-induced liver injury (DILI)

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.