14 June 2021

Safety Updates: Risk of TTS with Vaxzevria® (COVID-19 Vaccine AstraZeneca) and COVID-19 Vaccine Janssen®

1.0 Introduction:

The European Medicines Agency's (EMA) safety committee assesses and monitors the safety of medicines, including COVID-19 vaccines. The committee concluded its assessment of blood clots associated with Vaxzevria® **(**COVID-19 Vaccine AstraZeneca) on 7th April and COVID-19 Vaccine Janssen® on 20th April.

- The EMA has advised the overall benefits outweigh the risks for both vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®).
- After reviewing all available evidence; the EMA safety committee decided to list unusual blood clots with low blood platelets (termed Thrombosis with Thrombocytopenia Syndrome,TTS) as a very rare side effect of both vaccines.
- Anyone receiving these vaccines should be fully informed of the benefits and risks, including how to monitor for symptoms of this rare side effect.

The National Immunisation Advisory Committee (NIAC), is the expert group that advises on vaccination in Ireland. NIAC reviewed the EMA findings and issued revised advice on the use of the Vaxzevria® and COVID-19 Vaccine Janssen® in Ireland on 26 April 2021:

- Both vaccines are recommended for adults aged 50 years and over (including those with health conditions that puts them at very high or high risk of severe COVID-19).
- Because other vaccines are available, adults under the age of 50 (including those with health conditions that puts them at very high or high risk of severe COVID-19) will be offered the mRNA based vaccines.

2.0 Background:

- COVID-19 is a serious disease, caused by the SARS-CoV-2 virus, which has resulted in significant illness and death across the world including Ireland. COVID-19 vaccines have been developed and authorised for use after rigorous testing. The licensed vaccines have a favourable safety profile.
- More than 553,000 doses of Vaxzevria® have been given to people in Ireland so far, including frontline healthcare workers, and we can see the significant reduction in cases of COVID-19 disease in this group since the vaccine programme began.
- On 14 March 2021, NIAC recommended a temporary pause in the use of Vaxzevria®. This was because of a small number of cases of blood clots in people who had received the vaccine in European countries. These very rare blood clots were associated with low levels of blood platelets (platelets help blood to clot), with or without bleeding. Often these rare blood clots were in unusual locations including in the vessels draining blood from the brain (cerebral venous sinus thrombosis, CVST), the abdomen (splanchnic vein thrombosis) and in arteries. While the EMA investigated this, NIAC recommended pausing the use of the vaccine in Ireland pending the outcome. On 18 March 2021, the EMA safety committee's interim findings recommended the vaccine's benefits outweighed the risks. NIAC reviewed this information and recommended that vaccination with Vaxzevria® should recommence.
- On 7 April 2021, the EMA safety committee concluded its assessment and advised that the

overall benefits of the Vaxzevria® continue to outweigh the risks. However, it also decided to list unusual blood clots with low blood platelets (or TTS) as very rare side effects of Vaxzevria®. NIAC reviewed the EMA findings, the current situation in Ireland and recommended on 12 April 2021 that Vaxzevria® should not be used in people aged under 60 years (including those with health conditions that puts them at high risk and very high risk of severe COVID- 19).

- COVID-19 Vaccine Janssen® was authorised in the EU on 11th March 2021. Due to reports, of similar unusual blood clots with low platelets from the United States, EMA decided to investigate the COVID-19 Vaccine Janssen® before its roll out in Europe. These cases were similar to those investigated for Vaxzevria®. On 20th April 2021 the EMA safety committee concluded that the benefits of the vaccine in preventing COVID-19 outweigh the risks of very rare clotting events. However, they have advised that unusual blood clots with low blood platelets (or TTS) should be listed as very rare side effects of the vaccine.
- On 24th April 2021 the EMA released further analysis to help member states contextualise the risk of TTS and benefits of Vaxzevria® under different COVID-19 infection rates for different age cohorts. Available HERE.
- NIAC reviewed both these vaccines following the EMA investigations and updated their recommendations for Ireland in view of the current evidence and local situation. It revised the age restrictions for both vaccines on 26th April. **Currently both vaccines are recommended for those aged 50 and over.** NIAC issued an update about the interval between the first and the second dose on 13th May and further revised it on 31st May.
- The HSE is currently working to incorporate the recommended changes to the vaccination programme.

2.1 What has the EMA and NIAC recommended?

The EMA safety committee carried out a comprehensive review of these rare cases of blood clots. Read the EMA statement for Vaxzevria® HERE and COVID-19 Vaccine Janssen® HERE. Both reviews found that:

- The benefits of the vaccines in combating the threat of COVID-19 (which may also cause clotting problems, hospitalisation and may be fatal) continue to outweigh the risk of side effects

- Health professionals and those being vaccinated with Vaxzevria® or COVID-19 Vaccine Janssen® should be informed that TTS is a very rare side effect of the vaccines. People being offered these vaccines should be given patient information (provided by the HSE), on what to do in relation to these very rare events.

- Most cases of TTS occurred within 3 weeks of receiving the vaccine. The EMA has not specified any particular groups at higher risk of these rare side effects.

NIAC reviewed the EMA findings and current evidence within the local context. NIAC updated its recommended on 26 April 2021:

- Overall benefits of both vaccines outweigh the risks

- Vaxzevria® and COVID-19 Vaccine Janssen®:are recommended for those aged 50 years and older (including those with health conditions that puts them at very high or high risk of severe COVID-19).
- mRNA vaccines should be offered to those under the age of 50 (including those with health conditions that puts them at very high or high risk of severe COVID-19).
- However, where a two-dose mRNA vaccine schedule is not practical the single dose COVID-19 vaccine Janssen® can be offered to adults under the age of 50 (this recommendation is not currently being operationalised by the HSE).

On 26th April dose intervals were 12 weeks for all. However, those under the age of 50 without health conditions that puts them at high or very high risk of severe COVID-19 the dose intervals were increased to 16 weeks (as immunity is not known to wane for 16 weeks and NIAC were awaiting further data to assess risks and benefits of the second dose). On 13th May 2021 the dose interval was reduced to 12 weeks for all (including those under the age of 50 without high or very high risk conditions) as further data made available suggested the risk of TTS was lower after the second dose.

On 31st May 2021 dose intervals was further revised, the latest NIAC guidance recommends:

1. Individuals who have previously received a dose of Vaxzevria® to receive their second dose 8-12 weeks later (8 weeks preferred). A shorter interval (between 4 to <8 weeks) can be used in some situations e.g., pregnancy or imminent immunotherapy.
    - HSE is working to operationalise the reduction in dose interval to 8 weeks for everyone but this will take time. This is to ensure people have the best protection against COVID-19 quicker including against variants of concern such as the delta variant which is spreading rapidly in United Kingdom.

2. Those under the age of 50 who are immunocompetent but have previously had laboratory confirmed COVID-19 infection in the last 9 months a single dose of Vaxzevria® is needed to be considered fully immunised.
    - HSE is not operationalising this recommendation from NIAC. Everyone will be offered two appointments at the appropriate interval for a two dose COVID-19 vaccine regardless of prior COVID-19 infection status.

An additional contraindication for both vaccines was added by NIAC to include those who have been diagnosed with TTS after their first dose of Vaxzevria® or COVID-19 Vaccine Janssen® should not receive Vaxzevria® or the COVID-19 Vaccine Janssen®.

2.2 What information was reviewed by the European Medicines Agency (EMA) and the National Immunisation Advisory Committee (NIAC)?

For Vaxzevria® the EMA safety committee did an in-depth review of 86 cases (62 CVST cases and 24 splanchnic vein thrombosis cases; 18 of which were fatal) of unusual blood clots reported following vaccination to the European database (as of 22 March 2021) from European Economic Area (EEA) countries and the UK. The EMA safety committee also convened an ad hoc expert group to provide advice. Most of the cases occurred in women under the age of 60 in the first two weeks after vaccination. However, no specific risk factors were identified by the EMA. By 4 April 2021, nearly 34 million people have received the Vaxzevria® vaccine in the EEA and UK. There were 169 CVST cases and 53 splanchnic vein thrombosis cases reported to the European database. The risk of these unusual blood clots post vaccination remains very rare.

For COVID-19 Vaccine Janssen® the EMA reviewed eight reports (from the United States) of serious cases of TTS, one of which had a fatal outcome. Most of these rare events occurred within 3 weeks of receiving the first dose of the vaccine and in women under the age of 60. The EMA has not specified any particular groups at higher risk of these rare side effects**.** By the middle of April over 7 million people in the United States had received the COVID-19 vaccine Janssen®.

The EMA suggested that a potential biological mechanism for these rare side effects is due to the vaccine causing an immune response similar to that seen in another rare condition following injection with heparin (heparin induced thrombocytopenia, HIT).

The EMA safety committee has also asked for further research studies to provide more information

that will be reviewed.

However, due to the serious nature of these side effects (even though they are very rare), availability of other approved COVID-19 vaccines in Ireland and data suggesting that the benefits and risk of these vaccines may vary with age, NAIC updated its recommendations on the use of these vaccines in Ireland in certain ages.

Both EMA and NIAC agree these vaccines are effective at preventing COVID-19, reducing hospitalisation and deaths. It is important for both vaccinators and people who receive the vaccine to be aware of all the possible common, rare and very rare potential side effects of the vaccine.

If new information becomes available, the HSE will update all our colleagues, partners and information channels.

3.0 Questions and Answers:

3.1 How common are these unusual blood clots with low blood platelets or TTS?

Based on data from the EMA it is estimated that 1 in 100,000 people vaccinated with Vaxzevria® may develop TTS. 1 in 5 of these people who develop TTS may die. The risk of this very rare condition is higher in younger people.

Within the context of a medium background rate of infection, in adults aged 80 years and older it is estimated 197 deaths, 332 hospitalisations and 29 ICU admissions will be prevented for every 100,000 people that receive one dose of Vaxzevria®. In this same age group, the risk of TTS is 1 per 250,000 people vaccinated.

Based on data from the United States it is estimated that 1 in 300,000 people who are vaccinated with COVID-19 Vaccine Janssen® may develop TTS. 1 in 10 of these people who develop TTS may die. The risk of this very rare condition is higher in younger people. It is not yet known if there is an increased risk in women.

Overall benefits of both vaccines outweigh the risks.

3.2 What should I do if I am invited to receive Vaxzevria® or COVID-19 Vaccine Janssen® in the coming days?

You will be offered a COVID-19 vaccine in line with NIAC recommendations appropriate for your age.

Both EMA and NIAC agree these vaccines are effective at preventing COVID-19, reducing hospitalisation and deaths.

We would advise that you attend your appointment to receive your COVID-19 vaccine as soon as it is offered to you. Anyone being invited for vaccination is at higher risk of COVID-19 disease or is at high risk of serious illness and hospitalisation if they get COVID-19.

If you have questions about the vaccine, ask your vaccinator, or speak to a trusted healthcare professional such as your doctor or nurse. You can also find information on the HSE website:

3.3 As a healthcare worker, what should I do if I am invited to receive a COVID-19 vaccine?

You will be offered a COVID-19 vaccine in line with NIAC recommendations appropriate for your age. If you have never been vaccinated and you are aged under 50 years you will not be offered Vaxzevria® or COVID-19 Vaccine Janssen®. Health workers aged 50 and over can receive these vaccines.

Both EMA and NIAC agree these vaccines are effective at preventing COVID-19, reducing hospitalisation and deaths.

We would advise that you attend your appointment to receive your COVID-19 vaccine as soon as it is offered to you. As a frontline healthcare worker, you are at high risk of COVID-19 disease.

3.4 I've had one dose of Vaxzevria ®, what about a second dose?

Individuals (including those under the age of 50) who have received their first does of Vaxzevria® should receive their second dose 8-12 weeks after the first dose (unless there is a clinical contraindication) . There is no evidence of an increased risk of TTS after the second dose of Vaxzevria® (current evidence suggests the risk may be much lower after the second dose compared to the first dose).

The interval between the first and second dose can be reduced to between 4 to less than 8 weeks if required (e.g. if it allows for the schedule to be completed between 14-36 completed weeks of pregnancy or imminent immunotherapy)

NIAC has advised that individuals should complete the vaccine course with the same vaccine they received for the first dose. There is currently no data on the effectiveness of vaccination with two different vaccines.

However, those who are diagnosed with TTS after their first dose of Vaxzevria® should not have the second dose of Vaxzevria® or receive the COVID-19 Vaccine Janssen®.

3.5 Where can I get more information before I attend my appointment?

- Revised NIAC recommendations on the use of Vaxzevria® and COVID-19 Vaccine Janssen is available HERE.
- Read the Vaxzevria® vaccine Patient Information leaflet HERE.
- Read the COVID-19 Vaccine Janssen® Patient Information leaflet HERE.
- Information for patients on COVID-19 vaccines is available on the HSE website HERE.

3.6 What are the symptoms people should watch out for that may mean a blood clot?

Please seek prompt medical assistance and mention your recent vaccination if you get any of the following symptoms:

- breathlessness
- pain in the chest or stomach
- swelling or coldness in a leg
- severe or worsening headache (particularly 3 or more days after vaccination)
- blurred vision
- mental status changes (or confusion)
- seizures
- persistent bleeding under the skin where there was no injury
- multiple small bruises, reddish or purplish spots, or blood blisters under the skin,

The very rare blood clots with low platelets were usually reported within 3 weeks of getting Vaxzevria® or COVID-19 Vaccine Janssen®. You should watch out for these symptoms in the weeks after your vaccination.

3.7 I've had a first dose of Vaxzevria®, should I be concerned?

Vaxzevria® vaccine is effective at preventing COVID-19, reducing hospitalisation and deaths in all ages. The risk of TTS post vaccination remains very rare. You should watch out for the signs and symptoms of blood clots in the 3 weeks after your vaccination. Seek urgent medical help and mention that you have recently been vaccinated if you experience any of the symptoms

mentioned above (question 3.6).

3.8 What are the common side effects or symptoms people may get after receiving Vaxzevria® or COVID-19 Vaccine Janssen®?

We know that side effects of these vaccine usually happen in the first couple of days after the vaccine, and go away after a few days

After the vaccine, more than 1 in 10 people may experience:

- feeling tired
- tenderness, bruising, pain, redness or itching in the arm where they had the vaccine injection
- headache
- muscle pain
- joint pain
- nausea, diarrhoea or vomiting
- fever (temperature of 38 degrees Celsius or above)
- low blood platelets (that don't cause any symptoms)(for Vaxzevria®)

More than one in 100 people may have redness or swelling where they had the injection. It is common to develop a fever (temperature of 38 degrees Celsius or above) after any vaccination. This usually happens within 2 days (48 hours) of getting the vaccine. It usually goes away within 2 days. If you feel uncomfortable, take paracetamol or ibuprofen following the instructions on the box or leaflet.

You can find more details on uncommon and rare side effects within the vaccine specific information leaflets on our HSE website HERE

3.9 Is there anyone who should not get the Vaxzevria® or COVID-19 Vaccine Janssen vaccine®?

You should not receive the vaccines if you have had anaphylaxis (serious allergic reaction) following a previous dose of the vaccine or any of its ingredients (including polysorbate 80).

People are advised to delay the vaccine if they are sick with a fever (temperature of 38 degrees Celsius or above). You should also delay vaccination if you have had COVID-19 disease within the past 4 weeks.

In Ireland, most people under 50, will be offered the mRNA COVID-19 vaccines as these are the vaccines recommended by NIAC for this age group.

If you have had TTS after your first dose of Vaxzevria® vaccine you should not have the second dose of vaccine or the COVID-19 Vaccine Janssen.

You should not have Vaxzevria® if you have previously had capillary leak syndrome.

Read the full revised NIAC recommendations HERE.

3.10 What if I recently had a blood clot or I am on blood thinning treatments?

If you are eligible for the Vaxzevria® or COVID-19 Vaccine Janssen® as per the NIAC recommendations you can still have the vaccine if you have recently had a blood clot that is unrelated to vaccination or are on blood thinning treatments. There is no reason to delay vaccination. Like everyone who gets the vaccine, you should be aware of the symptoms to look out for.

3.11 What if I have a condition or I am on a treatment that may make me more likely to get a blood clot?

If you are eligible for the Vaxzevria® or COVID-19 Vaccine Janssen® as per the NIAC recommendations you can still have the vaccine. There is no reason to delay vaccination. Like everyone who gets the vaccine, you should be aware of the symptoms to look out for.

3.12 What if there is a history of blood clots in the family?

If you are eligible for the Vaxzevria® or COVID-19 Vaccine Janssen® as per the NIAC recommendations you can still have the vaccine. There is no reason to delay vaccination. Like everyone who gets the vaccine, you should be aware of the symptoms to look out for.

3.13 Can people choose to get a different vaccine instead of Vaxzevria® or COVID-19 Vaccine Janssen®?

At this time, supplies of the vaccines are limited so it is generally not possible to offer people a choice of COVID-19 vaccine. You will be offered a vaccine in line with NIAC recommendations. We recommend that people accept the vaccine that is offered to you to ensure you can be protected from COVID-19 as early as possible.

3.14 Should people take aspirin before or after vaccination?

No, these are very rare blood clotting conditions and aspirin would not have a beneficial effect. People do not need to start aspirin treatment before or after vaccination.

People should continue to take all prescribed medication unless advised by their medical practitioner.

3.15 What should healthcare workers do if they suspect a patient is experiencing a thromboembolism in the weeks after vaccination with Vaxzevria® or COVID-19 Vaccine Janssen?

Healthcare professionals should seek early expert advice from the National Coagulation Centre about the specialised testing and treatment options for patients presenting with thromboembolic events that are associated with thrombocytopenia, (including Disseminated Intravascular Coagulation (DIC) or Cerebral venous sinus thrombosis (CVST)) occurring within weeks following vaccination with Vaxzevria® or COVID-19 Vaccine Janssen®.

The EMA has recommended that anyone diagnosed with thrombosis after vaccination should be investigated for thrombocytopenia and similarly anyone diagnosed with thrombocytopenia should be assessed for thrombosis.

Read the Guidance on diagnosis and management of thrombocytopenia and thrombosis associated with adenoviral vector COVID19 vaccination HERE

Any suspected side effect linked to a COVID-19 vaccine should be reported to the Health Products Regulatory Authority (HPRA) HERE.