An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

# HPRA Safety Update

## COVID-19 Vaccines, Overview of National Reporting Experience

**Publication date: 22 April 2021 (Update #6)**

**Highlights from this update:**

- Up to 15 April, 6,616 reports of suspected side effects were notified to the HPRA. The cumulative figure of total doses of COVID-19 vaccines administered as of that date was reported as 814,470 (dose 1) and 341,129 (dose 2).[1]

- All vaccines have some side effects, the vast majority of which are mild to moderate in nature. These side effects need to be continuously balanced against the benefits in preventing COVID-19 illness. Overall, the national reporting experience continues to support the favourable assessment that the benefits of COVID-19 vaccines outweigh the risks.

- In the last month, the European Medicines Agency (EMA) have published safety update reports for all COVID-19 vaccines, including for Comirnaty® (on 29 March and 14 April), Moderna® (on 29 March), Vaxzevria® (previously called COVID-19 Vaccine AstraZeneca on 29 March and 14 April) and COVID-19 Vaccine Janssen® (on 14 April).

- The EMA's safety committee progressed a review of very rare cases of unusual blood clots occurring in combination with low platelets, and published recommendations for Vaxzevria® on 7 April and COVID-19 Vaccine Janssen® on 20 April. Product information for both vaccines has been updated to include important advice on this very rare but possible side effect. Healthcare professionals and those vaccinated should be aware of the remote possibility of developing this type of side effect, and recipients are advised to seek immediate medical attention if they develop symptoms and signs of bleeding or clotting. Further information, including a summary of national reports of blood clotting events, is provided in this update.

- The next HPRA safety update is due for publication on 20 May.

[1] *https://covid19ireland-geohive.hub.arcgis.com/*

## Understanding the data presented within this safety update

This update includes an overview of reports of ***suspected side effects*** notified to the HPRA safety monitoring system and is provided as an enhanced transparency measure for members of the public and healthcare professionals (HCPs). All vaccines have some side effects, the vast majority of which are mild to moderate in nature. These side effects need to be continuously balanced against the expected benefits in preventing COVID-19 illness.

Reports included in the overview are those notified to the HPRA on a voluntary basis by HCPs and members of the public, with reporting of suspected side effects to COVID-19 vaccines (www.hpra.ie/report) encouraged. Any reports of Irish cases received by the HPRA from the company (i.e. the licence holder, to date, BioNtech, Moderna, AstraZeneca, Janssen) responsible for the vaccine are also included within this update. This overview provides an up-to-date summary of national reporting experience.

However, it is important to understand that conclusions on the safety of a vaccine cannot be drawn based on the information provided, given well-established and known limitations in interpreting such data in isolation, examples of which are described below.

### Causation

- The HPRA receives reports based on ***suspicion*** that an adverse experience may be associated with vaccination. This does not mean the vaccine ***caused*** the adverse experience**.** As such, these are referred to as ***"suspected"*** side effects.
- Reports may describe coincidental events, which have occurred post-vaccination, but would have occurred even if vaccination had not taken place (e.g. they may be due to an underlying medical condition, or be signs and symptoms of another illness).
- Each individual report is carefully reviewed, however, the totality of data from all sources (e.g. clinical and epidemiological studies and literature) must be considered as part of ongoing safety monitoring to ensure ***evidenced based conclusions*** are drawn.

### Number/volume

- As the HPRA system is based on voluntary reporting, ***not all*** suspected side effects will be reported. As such, the number and types of reports notified can vary for a variety of reasons.
- An increased number of reports is expected for COVID-19 vaccines, given public interest as well as HPRA calls encouraging reporting. This is known as ***stimulated reporting***.
- A single report may describe more than one suspected side effect in an individual (e.g. headache and nausea reported together), therefore, the number of side effects may exceed the total number of reports received.

### Comparisons

- The type and number of reports received for different COVID-19 vaccines are ***not directly comparable*** as, for example, the vaccines have not been used in the vaccination programme for the same length of time, and will have been administered to different numbers of people, with different underlying medical conditions and across different settings.
- Each vaccine is authorised on the basis that its benefits-risk profile has and continues to be favourable.

### Changes to data over time

- The description of suspected side effects in this update reflects available information known at the time by the HPRA. These data may undergo changes as more information about individual reports becomes available through follow-up, and as more data are reported and evaluated.

For these reasons, the information in this report is not sufficient in isolation to draw conclusions on the safety profile of a vaccine. Like all vaccines, some side effects are to be expected, with the vast majority mild or moderate in intensity and resolving within a few days. Vaccines are approved for use on the basis of robust scientific evidence that demonstrates their benefits outweigh any risks.

***Always refer to the product information for information on the established safety profile, including known side effects of a COVID-19 vaccine.***

***This includes the Package Leaflet (for members of the public) and Summary of Product Characteristics (for healthcare professionals)***

Product information is accessible from
www.hpra.ie/homepage/medicines/covid-19-updates

## Authorised COVID-19 vaccines

COVID-19 vaccines currently authorised for use in the European Union by the European Medicines Agency include:

- Comirnaty® (licence holder: BioNTech), granted conditional marketing authorisation on 21 December 2020. For further information on this vaccine click here.
- COVID-19 Vaccine Moderna® (licence holder: Moderna), granted conditional marketing authorisation on 6 January 2021. For further information on this vaccine click here.
- Vaxzevria® (licence holder: Astra Zeneca), granted conditional marketing authorisation on 29 January 2021. For further information on this vaccine click here.
- COVID-19 Vaccine Janssen® (License holder: Janssen-Cilag International NV), granted conditional marketing authorisation on 11 March 2021. For further information on the vaccine click here. This vaccine has not yet been used in Ireland.

## Overview of suspected side effect reports

Up to 15 April, the HPRA received 6,616 reports of suspected side effects[2,3] in association with COVID-19 vaccines, as follows:

| | |
|---|---|
| Comirnaty® and COVID-19 Vaccine Moderna® (mRNA vaccines) | 3320 |
| Vaxzevria® (previously called COVID-19 Vaccine AstraZeneca | 3262 |
| Brand unknown/not specified | 34 |

The most regularly reported suspected side effects notified are as follows:[4]

| mRNA vaccines (Comirnaty® and COVID-19 Vaccine Moderna®) |
|---|
| **10% or more of reports describe:**<br>▪ Chills, fever, tiredness<br>▪ Dizziness, headache<br>▪ Muscle pain, pain (non-specific)<br>▪ Nausea<br><br>**1% to less than 10% of reports describe:**<br>▪ Abdominal pain, diarrhoea, tingling sensation in mouth, vomiting<br>▪ Altered taste, fainting, migraine, numbness, tingling/pins and needles, tiredness,<br>▪ Back pain, joint pain, limb pain, muscle weakness/stiffness, neck pain<br>▪ Chest discomfort/pain, feeling unwell, feeling hot/cold, flu-like symptoms, lack of energy/feeling weak,<br>▪ Cough, shortness of breath, sore throat<br>▪ Decreased appetite<br>▪ Enlarged lymph nodes<br>▪ Hives, itchiness, pale, sweating, rash<br>▪ Increased heart rate/racing heart<br>▪ Injections site redness, pain, swelling and itchiness<br>▪ Increased blood pressure<br>▪ Insomnia |

*[2] A single report may contain more than one suspected side effect for an individual (e.g. rash and hives reported together). Therefore, the total number of suspected side effects will exceed the total number of reports.*

*[3] In accordance with EU guidance, reports are valid if the minimum reporting criteria are met. These include an identifiable reporter, an identifiable patient, one or more suspected medicine known to be administered and one or more suspected adverse reaction.*

*[4]Terms listed as frequently reported are grouped according to standard coding classification system (MedDRA) adopted for use in the EU, presented by system organ class (SOC) and listed alphabetically. It should be noted that regular reporting of a side effect is not the same as the incidence of occurrence.*

| Vaxzevria® |
| --- |
| **10% or more of reports describe:**<br>▪ Fever, feeling cold, tiredness<br>▪ Dizziness, headache<br>▪ Joint pain, muscle pain, pain (non-specific)<br>▪ Nausea<br><br>**1% to less than 10% of reports describe:**<br>▪ Abdominal discomfort/pain, diarrhoea, vomiting<br>▪ Back pain, bone pain, limb discomfort, muscle spasms/weakness/stiffness, neck pain<br>▪ Chest discomfort/pain, feeling unwell, feeling cold/hot, flu-like symptoms, lack of energy/weakness,<br>▪ Cough, shortness of breath, sore throat<br>▪ Ear pain<br>▪ Enlarged lymph nodes<br>▪ Eye pain, vision blurred<br>▪ Fainting, migraine, numbness, tingling/pins and needles, tremor,<br>▪ Heart rate increased<br>▪ Increased heart rate/racing heart<br>▪ Injection site pain, redness, swelling, bruising<br>▪ Insomnia<br>▪ Lack of appetite<br>▪ Rash, sweating, itchiness |

These reports are consistent with the types of events typically observed following vaccination, including those described in the product information for the individual vaccines. The majority were mild to moderate in nature and had resolved/were resolving at the time of reporting.

In the following section, matters of interest regarding national reports and EMA safety related recommendations are provided.

## COVID-19 mRNA vaccines

### Reports of allergic type reactions (also known as hypersensitivity)

- Allergic type reactions are known side effects of mRNA vaccines. The EMA recently reviewed the different types of reactions reported, including from use in vaccination campaigns, and recommended an update to product information to include examples, such as skin rash and pruritus (itching of the skin), urticaria (raised, red and itchy skin rash) and angioedema (rapid swelling under the skin). The EMA noted that hypersensitivity reactions are generally uncommon (less than 1 in 100 persons), with urticaria and angioedema occurring rarely (less than 1 in 1,000 persons).
- In the context of suspected side effects notified to the HPRA, similar to the above, hypersensitivity reports such as itchiness, rash and hives are reported regularly, with cases of angioedema rarely described. The majority of reports are not of a serious nature, however, in some cases, medical treatment and/or clinical observation of the individual was required.

- The HPRA continue to closely monitor reports of anaphylaxis, which is a serious allergic reaction. Of the reports received, nine have been classified by the HPRA as anaphylaxis.[5] In all cases, the individual concerned was reported to have recovered.
- Anaphylaxis is a known side effect, and information on managing this risk is described in product information. As for all vaccines, COVID-19 vaccines should be administered under close supervision with appropriate medical treatment available in case of such a reaction.

### Reports of systemic events

- In a number of cases, reporters have commented on the impact on their normal daily activities of expected systemic events, similar to flu like symptoms, such as fatigue, headache, muscle/joint pain, chills and fever, in the day(s) following vaccination.
- Systemic events post vaccination are common, with the vast majority mild to moderate in nature and usually resolve within a few days of vaccination.
- These events may occur after either dose. However, the frequency and intensity observed in clinical trials was increased after the second dose of the mRNA vaccines.[6]

### Other recent product information updates recommended by the EMA

- Comirnaty®: Diarrhoea has been listed as a very common side effect (1 or more in 10 persons) and vomiting as a common side effect (less than 1 in 100 persons). Of the reports received by the HPRA, diarrhoea, vomiting and nausea, as well as abdominal discomfort are regularly reported. The vast majority of these events are mild or moderate in nature.
- Comirnaty®: Extensive swelling of the vaccinated limb, usually the upper arm, has been identified as a new side effect. The EMA have advised that although such swelling may appear severe to the vaccinated person, this condition usually recovers by itself within a couple of days after vaccination. The frequency of this side effect is being assessed further. The product information will be updated accordingly. Of the reports received by the HPRA, swelling at the injection site is regularly reported, however, reports of more extensive swelling are rare, with only a small number [7]received to date.

## Vaxzevria®

### Reports of blood clots in combination with low level of blood platelets

- Product information for Vaxzevria® was recently updated to list blood clots that occur in combination with a low level of blood platelets (cells that help the blood to clot) as a very rare but possible side effect. The types of blood clots seen have sometimes occurred in unusual locations (e.g. brain, bowel, liver, spleen). The majority occurred within two to three weeks following vaccination and were seen mainly in women under 60 years of age, although no specific risk factors have been confirmed.
- The update to product information follows a rigorous review by the EMA of cases observed from use in vaccination campaigns. Further information on the review is available through the EMA

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*[5]Reports classified using Brighton Collaboration case definition for anaphylaxis https://brightoncollaboration.us/category/pubs-tools/case-definitions/*

*[6]European Public Assessment Report (EPAR) for Comirnaty® available from the EMA website https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty*

*[7] When the relevant number is less than five, it is described as a small number to avoid any potential, inadvertant identification of the individuals concerned'*

website, including the recently published safety update report. The HPRA statement following the review is available here.

- Whilst the risk is very low, vaccine recipients should be aware of the remote possibility of developing this side effect. It is important that those vaccinated are aware of the updated advice, and are alert for signs and symptoms and know when medical attention should be sought. These include shortness of breath, chest pain, leg swelling, or persistent abdominal pain following vaccination. Those vaccinated are also asked to seek immediate medical attention if they experience after a few days severe or persistent headaches or blurred vision after vaccination, or skin bruising or pinpoint round spots beyond the site of vaccination which appears after a few days.
- The EMA has emphasised that these specific types of blood clots require specialised clinical management. HCPs may consult applicable guidance and/or specialists (e.g., haematologists, coagulation specialists) to diagnose and treat this condition. Information has been made available to HCPs (via the HPRA Drug Safety Newsletter and a Direct Healthcare Professional Communication) on the need to be vigilant for signs and symptoms in individuals recently vaccinated, and to report any suspected cases to the HPRA.
- The HPRA is closely monitoring reports of blood clotting events, including any occurring in combination with low platelets. As of 19 April, a total of 29 reports of blood clotting-type events were reported, of which a very small number[7] were in combination with low platelets. In these cases, the individuals concerned sought medical attention, received specialist medical care and are reported to be responding well to treatment.
- In relation to reports of blood clots without low platelets, the vast majority describe clots typically seen in the general population, such as those that occur in the legs (e.g. deep vein thrombosis), and lung (e.g. pulmonary embolism), for example. In many, the individuals concerned had risk factors for clotting. Similar types of blood clotting events (without low platelets) have been observed with mRNA vaccines, with 41 such reports received up to 19 April.

**Reports of allergic type reactions (also known as hypersensitivity)**

- The HPRA has received a number of reports of allergic type reactions associated with Vaxzevria®, which mainly describe symptoms such as itchiness, hives and rash. In a minority of cases, medical treatment and/or clinical observation of the individual was needed.
- The HPRA continue to closely monitor for reports of anaphylaxis, which is a serious allergic reaction. Of the reports received, a small number[7] have been classified by the HPRA as anaphylaxis[5]. In all case(s) the individual concerned was reported to have recovered.
- Anaphylaxis was recently added to the product information for Vaxveria® as a possible side effect, to reflect cases reported from use in vaccination programs. The EMA continues to review new information on anaphylaxis cases, as well as the different types of hypersensitivity reactions that occur.
- As for all vaccines, COVID-19 vaccines should be administered under close supervision with appropriate medical treatment available in case of such a reaction.

**Reports of systemic events**

- In a number of cases, reporters have commented on the impact on their normal daily activities of expected systemic events, similar to flu like symptoms, such as fatigue, headache, muscle/joint pain, chills and fever, in the day(s) following vaccination.
- Systemic events post vaccination are common, with the vast majority mild to moderate in nature and usually resolve within a few days of vaccination.

- These events may occur after either dose. However, adverse reactions reported after the second dose were milder and reported less frequently than after the first dose in clinical trials.

### Reports of deaths following vaccination

- A total of 40 reports have been submitted describing an individual who was known to be vaccinated and then subsequently passed away. Of these, 35 were reported with an mRNA vaccine. The types of events reported mainly include fatalities often seen in the general population, such as those due to natural causes or progression of underlying disease. In all cases, those concerned had underlying conditions and/or concurrent illness, with a small number having tested positive for COVID-19.
- Reports describing a death are carefully reviewed. However, it can be expected that fatalities due to progression of underlying disease or natural causes will continue to occur, including following vaccination. This does not mean that the vaccine caused the deaths. An EMA review of fatalities following mRNA vaccination did not identify a safety concern. In most cases, progression of (multiple) pre-existing diseases was considered a plausible explanation.

### COVID-19 Vaccine Janssen®

- This vaccine has not as of yet been administered in Ireland and as such, no data is included within this report. The HPRA statement on the EMA review of very rare cases of unusual blood clots that occurred in the United States, following the use of COVID-19 Vaccine Janssen, is available here.

## Further information on reports received by the HPRA

Reports received by the HPRA, including those not specifically described in this update, are available to the public via www.adrreports.eu. Whilst the vast majority of reports describe expected events (i.e. known side effects of a vaccine or vaccination process), reports can also be received for events that are unexpected and/or are considered serious as they required medical care or intervention. Such reports may describe events not caused by the vaccine and may have occurred coincidentally. However, all reports are carefully reviewed and if there is cause to do so, a further analysis is carried out to determine if a vaccine may have had a contributory role. If it is determined that a vaccine is a contributory factor, the public and healthcare professionals will be informed and the relevant product information will be updated.

The EMA publishes regular safety updates for COVID 19 vaccines, as well as highlights from meetings of the EMAs safety committee (Pharmacovigilance Risk Assessment Committee), which describe safety issues under review, as well as recommendations to revise product information. These are available via www.ema.europa.eu.

The EMA also make available anonymised information on all reports, including reports initially notified to the HPRA, publically available through the following link www.adrreports.eu and regularly publish recommendations made by the EMA Safety Committee (www.ema.europa.eu).

## Background information on the evaluation of suspected side effect reports

As for all medicines and vaccines, suspected side effect reports in association with COVID-19 vaccines submitted to the HPRA are recorded and stored on the HPRA's national adverse reactions database. They are subsequently submitted (with any personal identifiers and contact details removed) to the EudraVigilance database operated and managed by the European Medicines Agency (EMA). EudraVigilance provides for the transfer of reports from national regulatory agencies such as the HPRA and marketing authorisation holders to the EMA, and supports early detection and monitoring of possible safety signals in relation to reported side effects.

The EMA also make available anonymised information on all reports, based on global safety experience, publically available through the following link www.adrreports.eu and regularly publish recommendations made by the EMA Safety Committee (www.ema.europa.eu).

Information from side effect reports, together with additional safety data (e.g. from the scientific literature, cumulative safety data analysis, epidemiological studies etc.) are assessed on an on-going basis, in conjunction with our EU counterparts to consider their impact on the known safety profile of the COVID-19 vaccines and any need for regulatory changes to support safe and appropriate use.

Partially anonymised details of reports are also shared with other bodies also involved in safety monitoring of medicines, in accordance with the legislative provisions, including GDPR (please see the HPRA privacy statement here). These bodies include the World Health Organisation (WHO) and as appropriate, the company(ies) that hold the licence(s) for the medicine(s) concerned (i.e. marketing authorisation holders or 'MAHs'). Sharing of this information ensures that the information is available to all parties responsible for the ongoing safety monitoring of medicines.

Further information to support interpretation of the data provided in this update is available here