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August highlights from the Pharmacovigilance Risk Assessment Committee (PRAC)

Conclusions and recommendations regarding COVID-19 vaccines and therapies

Vaxzevria® and Guillain-Barré syndrome

The PRAC has continued assessing cases of Guillain-Barré syndrome (see previous issue) reported after administration of Vaxzevria® and included in the MAH's monthly safety report. The vaccine's benefit/risk profile remains unchanged.

COVID-19 Vaccine Janssen: immune thrombocytopenia, dizziness

The PRAC has recommended that the SmPC and PL of this vaccine be updated to include immune thrombocytopenia as an adverse reaction. An alert should be issued to inform healthcare professionals.

Following assessment of 1,183 instances of dizziness in spontaneously reported cases of vaccination-related anxiety, as well as of 6 cases of dizziness in clinical trials and 108 cases of spontaneous reports of unilateral or bilateral tinnitus, the PRAC has further recommended that the product's information be updated to include dizziness and tinnitus as listed adverse reactions. The vaccine's benefit/risk profile remains unchanged.

Other safety issues

The PRAC has discussed reported cases of **menstrual cycle disorders** following COVID-19 vaccination. **No causal relation** has been so far established.

Menstrual disorders are very common and can occur with no underlying medical condition. Causes vary from stress and fatigue to clinical conditions such as uterine fibromyomata and endometriosis.

Vaccinated women presenting with unexpected vaginal bleeding (e.g., postmenopausal women) or who are concerned about prolonged or intense vaginal bleeding should contact their physician for advice. This issue will keep being monitored.

Márcia Silva

INDEX CARD

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ADRs in the Literature
Hypersensitivity reactions to COVID-19 vaccines

In this review published in the Acta Médica Portuguesa, the authors (from the Coimbra University Hospitals) present an overview of the various types of hypersensitivity reactions (HRs) that can supervene in association with anti-COVID-19 vaccines.

Although any one vaccine component can theoretically trigger an HR and the role of vaccine antigens themselves is still uncertain, adjuvants and excipients are the main culprits.

The excipients of vaccines currently in use in Portugal are as follows:

Vaccine (click on the trademark name for a complete list of excipients)	**Possibly allergenic excipients**
Comirnaty *(mRNA)*	**PEG2000**
Spikevax *(mRNA)*	**PEG2000, Trometamol (Tromethamine)**
Vaxzevria *(adenoviral vector)*	**Polysorbate 80 (E 433)**
covid-19 Vaccine Janssen *(adenoviral vector)*	**Polysorbate 80 (E 433)**

Polyethylene glycol (PEG) is widely used in pharmacy, cosmetics and household products. It is a component of tablets, suppositories, ointments, injectables, gels and lubricants. Because it is inert and poorly absorbed, PEG (or macrogol) is also the active ingredient of laxatives and bowel prep agents for diagnostic exams.

Rare cases of immediate and delayed HRs with PEG can be found in the literature. Molecular weight is relevant, since low molecular weight (200-700 Da) PEG is mostly associated with contact dermatitis and urticaria, whereas higher molecular weight PEG (1,000-7,500 Da), which includes the excipient in COVID-19 mRNA vaccines, is implicated in cases of anaphylaxis.

The typical patient with an HR to PEG has a history of multiple reactions to medicinal products of various classes while possibly no reaction to the same medicine of a different brand or formulation.

Polysorbates are part of the composition of various commonly used medicinal and other products, including vaccines (e.g., hepatitis B, rotavirus, HPV, pneumococcus, influenza), biologics, monoclonal antibodies and chemotherapeutic agents. The clinical manifestations of HRs to polysorbates range from contact dermatitis to urticaria and anaphylaxis.

Tromethamine (trometamol) can also trigger HRs, though evidence is thinner.

Liposomes can activate the immune system by inducing an inflammatory response with cytokine release.

It is also possible that both **messenger RNA** and **adenoviral vectors** in anti-COVID-19 vaccines are immunogenic and can trigger HRs or hypersensitivity-like reactions. In fact, exacerbated reactogenicity can initiate an immune cascade which, in turn, can activate the immune system in an aberrant way.

An **HR following a first dose of vaccine** can sometimes be difficult to determine. The authors of this review propose that individuals who have sustained a life-threatening reaction, namely anaphylaxis, should not receive a second dose of the same vaccine, nor of another vaccine with similar excipients. In the case of milder reactions, such as localized urticarial reactions, pre-treatment with an anti-histamine before the second dose is often proposed; administration should be undertaken in facilities with cardio-respiratory resuscitation capabilities and a post-inoculation wait time of 30 minutes to one hour should be ensured.

Serum tryptase dosing in blood collected 30 minutes to two hours post adverse reaction can help to confirm a diagnosis of anaphylaxis, since tryptase is a mastocyte activation (degranulation) biomarker. Skin prick tests, on the other hand, should not be performed earlier than four weeks after the event.

Data on the mechanisms of possible COVID-19 vaccine HRs are still limited. Intensive monitoring of these vaccines is ongoing. The authors of this article believe that adequate classification and causality assessment of suspected HRs are essential for effective clinical management and for counteracting misinformation and vaccination hesitancy.

• Carvalho JC et al. Hypersensitivity reactions to vaccines: current evidence and standards for sars-cov-2 vaccines. Acta Med Port 2021 Jul-Aug;34(7-8):541-547. https://doi.org/10.20344/amp.16096

Communications to Healthcare Professionals published on the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Communication? Online publication date
Tofacitinib *Xeljanz*	**Physicians:** rheumatology, internal medicine and dermatology (rheumatoid arthritis and psoriatic arthritis clinics); gastroenterology (ulcertaive colitis)	Increased risk of major adverse cardiovascular events and malignant neoplasms with TNF-alpha inhibitors 06-07-2021
COVID-19 mRNA vaccine (with modified nucleoside) *Comirnaty* *Spikevax*	**Healthcare professionals:** vaccination centres, general/family medicine, internal medicine, cardiology, emergency services, Portuguese National Health Service 24-hr Helpline, and Portuguese Society of Cardiology	Risk of myocarditis and pericarditis 19-07-2021
COVID-19 non-replicating viral vector vaccine (type 26 human adenovirus) *COVID-19 Vaccine Janssen*	**Healthcare professionals:** vaccination centres, internal medicine, general/family medicine, clinical haematology, immuno-haemotherapy, intensive care units, hospital emergency services, and Portuguese National Health Service 24-hr Helpline	Contraindication in individuals with a history of capillary leak syndrome, and update on thrombosis with thrombocytopenia syndrome 19-07-2021
Varenicline *Champix*	**Physicians:** primary care and family medicine units, cardiology, respiratory medicine, psychiatry, Portuguese Society of Pneumology, Portuguese General/Family Medicine Association and Portuguese Respiratory Diseases Study Group **Pharmacists:** hospital and community	Batch withdrawal due to presence of an N-nitroso-varenicline impurity above calculated acceptable daily intake 15-07-2021

Compiled by Patrícia Catalão

Educational Materials publishedon the Infomed product information webpage

Clique nas hiperligações para consultar

INN Medicinal product	Target	Materials? Online publication date
Elvitegravir + Cobicistat + Emtricitabine + Tenofovir *Stribild*	**Physicians:** infectious diseases, internal medicine, paediatrics (follow-up of HIV-infected patients), and hospital paediatrics dpt directors	Recommendations on kidney and bone risk management 16-07-2021
Gilteritinib *Xospata*	**Physicians:** haematology	Guide: risk of differentiation syndrome 06-07-2021
Tolvaptan *Jinarc*	**Physicians:** nephrology **Patients**	Information guide Prescription checklist Educational brochure Alert card 08-07-2021

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ADRs in the Literature

ADR reporting by patients: do personal feelings and opinions matter?

This is one of the still relatively few descriptive studies on ADR reporting by patients. It consisted of an analysis of the reports sent to the Catalan Pharmacovigilance Centre between 2013 and 2017. A total of 190 reports were sent through by patients in that period (corresponding to 4% of the overall total number of reports received by the centre). Patient mean age was 39 years (between 1 and 86 years) and almost two thirds were female. The most frequent ADRs were GI and neurological (19% each) and the class of nervous system medicines was most frequently implicated.

In **40%** of cases, the patient filled in the report's **free text** section. In one fourth, additional useful data were provided, namely regarding the bio-psychosocial impact of the adverse effects, which may account for the **discrepancy in seriousness classification** between patients and healthcare professionals. In fact, though seriousness perception agreement between the two groups was considered "good", over one third (37 of 99) of ADRs viewed as serious by patients were classified as clinically non serious by the pharmacovigilance team. Although 62% of the free text comments included notes that were useful input for the causality assessment algorithm, around **38% described personal points of view and even private feelings**.

Free text and personal comments do not typically match any of the ADRs listed in the SmPCs and PLs of medicines. However, when healthcare professionals ignore or devalue the relevance of those comments, patients can be driven to seek solutions by themselves, such as **by discontinuing treatment or by taking additional medicines** for unpleasant symptoms or sensations.

In the last few years patients have taken on an active role in medicinal product safety monitoring systems, namely through "first-hand" ADR reporting. According to the authors of this study and similarly to others, in spite of some initial reticence, patient contribution has been proving useful. The authors believe that the inclusion of data on ADR social and emotional impact in seriousness assessment algorithms should be pondered.

• Riera-Arnau J et al. Patients' contribution to drug safety in Catalonia: the interest of personal feelings on adverse drug reactions. Eur J Clin Pharmacol 77, 637–642 (2021). https://doi.org/10.1007/s00228-020-03033-5

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics