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April and May highlights from the Pharmacovigilance Risk Assessment Committee (PRAC)

Conclusions and recommendations regarding COVID-19 vaccines

Vaxzevria®, COVID-19 Vaccine Janssen:

Following assessment of all available data, including an ad-hoc expert group opinion, the PRAC concluded in April that the **very rare** occurrence of unusual blood clots combined with low platelets **(thrombosis with thrombocytopenia syndrome – TTS)** should be included in the SmPC and PL of Vaxzevria® (formerly known as COVID-19 Vaccine AstraZeneca®). The same conclusion came to be applied in May to COVID-19 Vaccine Janssen® (at this time still only used in the USA but already with marketing authorization for the EU since March). Four analogous cases were reported concerning this vaccine too.

EMA and INFARMED have previously alerted healthcare professionals and vaccinated persons to look out for any suspicious signs and symptoms **in the two weeks following vaccination**. Changes to the SmPC/PL texts have also been recommended regarding monitoring for signs and symptoms of thrombosis in patients presenting with **thrombocytopenia in the 3 weeks following vaccination.** Conversely, patients with **thromboembolic phenomena in the 3 weeks following vaccination** should be assessed for the presence of thrombocytopenia.

Comirnaty®, COVID-19 Vaccine Moderna®

As for mRNA vaccines, assessment of the low number of cases reported of thromboembolic events with thrombocytopenia with no specific clinical pattern, contrarily to the events reported with non-replicating viral vector vaccines, has led the PRAC to conclude that a causal nexus cannot be defined at this time. Close monitoring will continue.

On the other hand, it has been concluded that there is a possible causal relation between the occurrence of **facial oedema in persons with a history of skin filling injections** and Comirnaty®. For this reason, the PRAC has recommended the inclusion of this adverse reaction in the vaccine's product information.

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April and May highlights from the Pharmacovigilance Risk Assessment Committee (PRAC)

New assessments starting for COVID-19 vaccines

Vaxzevria®

The PRAC has started the **assessment** of a possible safety signal arising from five cases of **capillary transudation**, a very rare syndrome characterized by fluid leaking from blood vessels resulting in tissue oedema and blood pressure drop.

Additionally, the PRAC is **assessing** cases of **Guillain-Barré syndrome** following vaccination. This autoimmune disorder causes nerve inflammation and initially results in pain, numbness, muscle weakness and difficulty walking.

Comirnaty®, COVID-19 Vaccine Moderna®

Cases of myocarditis (heart muscle inflammation) and pericarditis (inflammation of the membrane enveloping the heart) have been reported to EMA mostly following vaccination with Comirnaty®. For the time being there is no evidence that these cases could have been caused by the vaccines. However, detailed case analysis by the MA Holders of both vaccines has been requested within the scope of their monthly safety reports. The EMA will report as soon as new additional information is available.

Márcia Silva

Communications to Healthcare Professionals published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Communication? Online publication date
Aflibercept *Eylea, 40 mg/ml solução injetável em seringa pré-cheia*	**Physicians:** ophthalmologists at hospitals and clinics, Portuguese GMC College of Ophthalmology and Portuguese Society of Ophthalmology **Pharmacists:** hospital	Higher risk of raised intraocular pressure with the pre-filled syringe 15-04-2021
Non-replicating viral vector (human adenovirus type 26) anti-COVID-19 vaccine *COVID-19 Vaccine Janssen*	**Healthcare professionals:** vaccination centres, internal medicine, general/family medicine, clinical haematology, immune-haemotherapy, intensive care units, hospital emergency services, and Portuguese National Health Service 24-hr Helpline	Plausible causal relation between the vaccine and thrombosis in combination with thrombocytopenia 26-04-2021
Non-replicating viral vector (chimpanzee adenovirus) anti-COVID-19 vaccine *Vaxzevria (anteriormente COVID-19 Vaccine AstraZeneca)*	**Healthcare professionals:** vaccination centres, internal medicine, general/family medicine, clinical haematology, emergency services, and Portuguese National Health Service 24-hr Helpline	Plausible causal relation between the vaccine and thrombosis in combination with thrombocytopenia 13-04-2021
Voriconazole *Vfend, 200 mg pó para solução para perfusão*	**Pharmacists:** hospital pharmacy service directors	Current shortage in EU member states 26-04-2021

Compiled by Patrícia Catalão

Lamotrigine
photosensitivity risk

Quick Read
Photosensitivity reactions have been reported in association with lamotrigine, usually following a high dose or a dose increase. In these cases, discontinuing the drug should be considered. If stopping the treatment is clinically inadvisable, sun exposure protection measures need to be reinforced.

Lamotrigine is a second generation antiepileptic agent belonging to the phenyltriazine class. It is indicated in the treatment of epilepsy in association therapy or in monotherapy, as well as in bipolar disease in the prevention of depressive episodes in patients with bipolar disease I who have predominantly depressive episodes.

Drug-induced photosensitivity produces skin lesions caused by the simultaneous effects of a drug (either topical or systemic) and of exposure to UV radiation. Photosensitivity reactions can be classified into phototoxic or photoallergic.

Phototoxic reactions are more common and result from ultraviolet light activation (transformation or degradation) of photo-reactive substances that thus become toxic for skin cells. These reactions have the appearance of an exacerbated solar burn, supervene shortly (hours) after exposure and in exposed skin only.

Photoallergic reactions, on the other hand, are type IV or delayed hypersensitivity reactions. They appear slowly as eczematous, pruritic skin rashes and may not be restricted to exposed skin. In photoallergy a drug photo-binds to a protein (hapten) and the resulting antigen triggers a cell-mediated immune response.

Because photosensitivity reactions associated with the use of lamotrigine have been reported, some of which severe and leading to hospitalization and change of therapy, the EMA has conducted a review of all cases in the European adverse drug reaction database EudraVigilance (EVDAS) and in the literature. Given these cases and lamotrigine's mechanism of action, it was concluded that there was sufficient evidence to confirm a causal nexus between lamotrigine and photosensitivity. This has prompted an update of the SmPCs and PLs of the products containing lamotrigine as an active substance. In addition to the pre-existing warning on skin rashes, the following will be included in **SmPC section 4.4 on Warnings and special precautions:**

> There have also been reports of photosensitivity reactions associated with lamotrigine use (see section 4.8). In several cases, the reaction occurred with a high dose (400mg or more), upon dose escalation or rapid up-titration. If lamotrigine-associated photosensitivity is suspected in a patient showing signs of photosensitivity (such as an exaggerated sunburn), treatment discontinuation should be considered. If continued treatment with lamotrigine is considered clinically justified, the patient should be advised to avoid exposure to sunlight and artificial UV light and take protective measures (e.g. use of protective clothing and sunscreens).

João Paulo Fernandes

What do they mean

AIM	Autorização de Introdução no Mercado – em inglês ***MA*** *Marketing Authorisation*
EMA	Agência Europeia do Medicamento – do inglês *European Medicines Agency*
FI	Folheto Informativo – em inglês *PIL Patient Information Leaflet*
PRAC	Comité de Avaliação do Risco em Farmacovigilância (da EMA) – do inglês *Pharmacovigilance Risk Assessment Committee*
RAM	Reação Adversa a Medicamentos – em inglês ***ADR*** *Adverse Drug Reaction*
RCM	Resumo das Características do Medicamento – em inglês ***SmPC*** *Summary of Product Characteristics*

Educational Materials published in the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials? Online publication date
Avelumab *Bavencio*	**Patients**	Information brochure Alert card 17-04-2021
Deferasirox *Exjade, comprimido revestido por película*	**Physicians:** immune-haemotherapy, haematology and paediatrics department directors of hospitals procuring this medicinal product	Posology and biologic monitoring checklist 17-04-2021
Lenalidomide *Revlimid*	**Physicians:** haematology **Pharmacists:** pharmaceutical services at units where the product is prescribed and dispensed.	Safety information Spontaneous safety information reporting form (adverse events, events associated with special conditions and pregnancy related information) Pregnancy notification form
	Patients	Booklet for women of childbearing potential Booklet for women without childbearing potential Booklet for male patients 17-04-2021
Vismodegib *Erivedge*	**Physicians:** dermatology, oncology, plastic surgery and radiotherapy (hospitals where the product can be expected to be prescribed) **Patients**	Patient guidance Information card Brochure: important information on pregnancy prevention and contraception, for females and males 05-03-2021

Compiled by Patrícia Catalão