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June/July highlights from the Pharmacovigilance Risk Assessment Committee (PRAC)

Ongoing assessments and conclusions regarding COVID-19 vaccines and therapies

Very rare cases of myocarditis and pericarditis can occur in persons vaccinated with Comirnaty® and Spikevax®

By 31st May 2021, 177 million doses of Comirnaty® and 20 million doses of Spikevax® (previously COVID-19 Vaccine Moderna®) had been administered in the European Union (EU).

The PRAC has analyzed in detail 164 cases of myocarditis that occurred in the EU in patients who received mRNA technology COVID-19 vaccines, namely 145 with Comirnaty® and 19 with Spikevax®. Cases that occurred elsewhere in the world (in Israel at first) were also assessed.

Most cases supervened in the **first 14 days post-vaccination**, more often following the second dose and in young adult males. Five cases in elderly persons or in patients with other morbidities culminated in death. In general, however, data indicate that the evolution of post-vaccine myocarditis and pericarditis is similar to the typical clinical course of those two conditions, which usually resolve with rest or with treatment.

The PRAC has concluded that myocarditis and pericarditis should be listed in the SmPCs as adverse reactions of mRNA technology vaccines.

Further information can be found on this Infarmed Circular.

Myocarditis and pericarditis are inflammatory heart conditions affecting the cardiac muscle and the heart's membrane (pericardium), respectively. They can occur after an infection or be associated with immune system conditions. They are usually self-limited and resolve with treatment. Symptoms are diverse but commonly include breathlessness, chest pain and palpitations (which can be irregular).

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Guillain-Barré Syndrome and Vaxzevria® and COVID-19 Vaccine Janssen®

During the assessment of both Vaxzevria® and COVID-19 Vaccine Janssen®, Guillain-Barré syndrome (GBS) was tagged as an event requiring special monitoring attention.

Following assessment of all available data, the PRAC decided that a definitive conclusion cannot be reached whether there is a causal nexus between GBS and the above two vaccines.

However, given the seriousness of GBS, an alert has been inserted in the vaccines' SmPC/PL to raise the awareness of healthcare professionals and patients about the possibility of this potential risk. Healthcare professionals should look out for early signs and symptoms so a timely diagnosis can be made and adequate treatment given. Vaccinated individuals should be instructed to contact their doctor promptly in case they develop limb weakness or palsy, possibly progressively affecting the neck and face.

The benefit/risk balance of these two vaccines remains unaltered. The PRAC will keep following up on the risk of GBS and will take any additional measures if necessary.

Guillain-Barré syndrome is an immune disorder that causes nerve inflammation. The first manifestations are usually limb numbness, tingling and muscle weakness, followed by difficulty walking. More serious forms can progress to generalized paralysis and can be life threatening. Early treatment can reduce symptom intensity and duration.

Vaxzevria® and Janssen® vaccines contraindicated in persons with a history of capillary leak syndrome

By 27th May 2021, over 78 million doses of Vaxzevria® had been administered in the EU and the UK.

The PRAC has analyzed 14 cases of suspected capillary leak syndrome in persons who had received Vaxzevria®, in six of whom the diagnosis was confirmed. Most occurred in women in the four days following vaccination and three (including one fatality) had a past history of capillary leak syndrome.

There were three additional cases (two of which fatal) in persons vaccinated with COVID-19 Vaccine Janssen®. They all occurred up to two days after inoculation and in one case there was a past history of capillary leak syndrome.

Although it is not yet possible to definitively conclude that there is a causal relation, the PRAC has recommended that capillary leak syndrome be listed as a new adverse reaction in the SmPC/PL of both vaccines, together with an alert for healthcare professionals and patients.

The PRAC will keep following up this risk and will take any additional measures if necessary. Further information can be obtained from the Infarmed Circulars regarding both Vaxzevria and COVID-19 Vaccine Janssen.

Capillary leak syndrome is very rare and potentially serious. It is characterized by leakage of fluids from the blood vessels resulting in tissue oedema and a drop in blood pressure.

Veklury® (remdesivir): sinus bradycardia to be listed as adverse reaction (of unknown frequency) in the SmPC and PL

The PRAC has concluded from the available data that there is a possible causal nexus. Most cases of sinus bradycardia resolved upon treatment discontinuation.

Veklury® is indicated for the treatment of COVID-19 in adults and adolescents (aged 12 years or more and weighing at least 40 kg) with pneumonia requiring oxygen supplementation.

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Conclusions from the assessment concerning Xeljanz® (tofacitinib)

Xeljanz® (tofacitinib) is a Janus kinase (JAK) inhibitor, indicated for the treatment of:

- moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs);

- adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent

Following assessment of the data from a study in patients older than 50 years and with at least one associated cardiovascular factor, who showed increased risk of major adverse cardiovascular events and malignant neoplasms when compared with other TNF-alpha inhibitors, the PRAC recommends that Xeljanz® should be used in patients:

- older than 65 years of age
- who are current or past smokers
- with cardiovascular risk factors
- with risk factors for malignant neoplasms,
only in case there is no alternative treatment.

The product's benefit/risk balance should be carefully assessed for each individual patient before therapy with tofacitinib is prescribed or continued.

Márcia Silva

Communications to Healthcare Professionals published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Communication? Online publication date
Non-replicating viral vector (chimpanzee adenovirus) COVID-19 vaccine *Vaxzevria previously COVID-19 Vaccine AstraZeneca*	**Healthcare professionals:** at vaccination centres, general/family medicine, emergency services, internal medicine, haematology and Portuguese NHS 24-hr helpline	Risk of thrombosis with thrombocytopenia - update Contraindication in persons with capillary leak syndrome 02-06-2021
Venetoclax *Venclyxto*	**Physicians:** haematologists	Updated recommendations on tumour lysis syndrome in patients with chronic lymphocytic leukaemia (CLL) 09-06-2021

Compiled by Patrícia Catalão

ADRs in the Literature

Potential association between COVID-19 mRNA vaccines and facial palsy probably similar to other antiviral vaccines

Occasional cases of isolated facial palsy (with no other neurological manifestations or complications) have long been reported following administration of various antiviral vaccines. It is still uncertain whether a causal nexus exists. It is thought that immune activation or latent viral infection (such as herpes) reactivation may be at play. In this type of context facial palsy is typically unilateral and resolves spontaneously.

During COVID-19 mRNA vaccine clinical trials, **rare cases** of facial palsy were observed. There were seven cases, of which six with facial palsy appearing **3 to 48 days after** the second dose of the vaccine and one in which the palsy supervened 37 days after the first dose (with no second dose having been administered).

Disproportionality analyses are hypothesis generating methodologies for the detection of associations between medicinal products and adverse reactions. Since quantitation of the total population that has actually been exposed to the medicine is not available, it is not possible to quantify risks either. However, disproportionality analyses are able to quantify the extent to which the frequency of a drug-event combination is out of proportion to what could be expected should no association exist.

The authors of this April 2021 Letter to the JAMA (Journal of the American Medical Association) Internal Medicine Editor have undertaken four disproportionality analyses on the **World Health Organization pharmacovigilance database (VigiBase)**, using two control groups – one of individuals exposed to influenza vaccines, another of individuals exposed to all other antiviral vaccines.

When compared with other viral vaccines, COVID-19 mRNA vaccines (until March 9th 2021 when 320 million doses had already been administered worldwide) were not associated with a facial palsy reporting rate higher than that observed for other viral vaccines. Even allowing for possible biases and confounding factors, the authors have concluded that the risk of facial palsy, if any, is probably very low and comparable to that of other antiviral vaccines.

• Renoud L et al. Association of Facial Paralysis With mRNA COVID-19 Vaccines: A Disproportionality Analysis Using the World Health Organization Pharmacovigilance Database. JAMA Intern Med. 2021 Apr 27:e212219

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

Educational Materials published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials? Online publication date
Alglucosidase alfa *Myozyme*	**Healthcare professionals:** physicians, nurses and pharmacists involved in the treatment of Pompe disease	Guide on administration-associated risks, clinical risk management and immunogenicity testing 01-05-2021
Brigatinib *Alunbrig*	**Patients**	Alert card 22-06-2021
Dabigatran etexilate *Pradaxa*	**Physicians:** general/family medicine, immuno-haemotherapy, cardiology, internal medicine and paediatrics (including cardiology, haematology, oncology and neonatology)	Paediatric prescription guide 03-06-2021
Darbapoetin alfa *Aranesp, prefilled syringe*	**Physicians:** haematology, oncology and nephroloy directors at hospitals and clinics procuring this medicine **Visually impaired patients/caregivers**	Checklist for training on self-administration Instructions for use poster 05-05-2021
Emtricitabine + Tenofovir *Emtricitabina + Tenofovir Farmoz*	**Physicians:** infectious diseases, internal medicine, gastrenterology and paediatrics **Physicians:** potential PrEP (pre-exposure prophylaxis) prescribers - infectious diseases, internal medicine, paediatrics **At-risk individuals**	Recommendations: treatment of adolescents with chonic hepatitis B and/or HIV-1 infection Educational brochure on PrEP PrEP checklist Educational borchure on PrEP PrEP reminder card 18-05-2021
Fingolimod *Gilenya*	**Physicians:** neurologists, neuropaediatricians and GYN/OBS involved in the treatment of multiple sclerosis **Patients**	Prescribing physician's checklist Guide 08-06-2021

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INN Medicinal product	Target	Materials? Online publication date
Glucagon *Baqsimi*	**Healthcare professionals:** endocrinology (including paediatric endocrinology), authorized insulin pump centres and Núcleo de Estudos de Diabetes Mellitus healthcare professionals	Demo device leaflet
	Patients	Administration leaflet 18-06-2021
Hydroxycarbamide *Siklos*	**Physicians:** haematology and paediatrics	Treatment guide – sickle cell anaemia
	Patients	Guide – sickle cell anaemia 10-06-2021
Inotersen *Tegsedi*	**Patients**	Alert card 03-06-2021
Ipilimumab *Yervoy*	**Patients**	Guide Alert card 03-06-2021
Leuprorelin *Eligard*	**Healthcare professionals:** urology, oncology and internal medicine dpts; hospital pharmacy services; nursing services	Preparation instructions Preparation video 22-06-2021
Levonorgestrel *Jaydess* *Kyleena* *Mirena*	**Physicians:** Gyn/Obs and general/family medicine physicians undertaking family planning clinics	Risk of ectopic pregnancy, and distinguishing between intrauterine release devices with levonorgestrel 29-06-2021
Micafungin *Micafungina Teva*	**Physicians:** infectious diseases, intensive medicine, general surgery, microbiology, transplantation unit and paediatrics dpt directors	Prescription checklist 17-06-2021
Pembrolizumab *Keytruda*	**Patients**	Guide Alert card 19-05-2021
Ranibizumab *Lucentis*	**Patients**	Guide Audioguide 30-06-2021

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INN Medicinal product	Target	Materials? Online publication date
Tenofovir *Tenofovir Aurovitas, Tenofovir Farmoz*	**Physicians:** infectious diseases, internal medicine, gastroenterology and paediatrics	Recommendations: treatment of adolescents with chonic hepatitis B and/or HIV-1 infection 18-05-2021
Tiotropium bromide *Sirkava*	**Physicians:** respiratory medicine and general/family medicine	Guide 28-05-2021
Trastuzumab deruxtecan *Enhertu*	**Physicians:** oncology **Nurses:** oncology **Pharmacists:** hospital	Healthcare professional guide (interstitial pulmonary disease/ pneumonitis) Healthcare professional guide for the prevention of medication errors resulting from product mix-ups
	Patients	Card – potential lung problems 18-06-2021

Compiled by Patrícia Catalão