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August/September highlights from the Pharmacovigilance Risk Assessment Committee (PRAC)

Ongoing assessments and conclusions regarding COVID-19 vaccines

COVID-19 vaccines in general and multisystem inflammatory syndrome

The PRAC has initiated a safety assessment prompted by reports of cases of multisystem inflammatory syndrome (MIS) following administration of COVID-19 vaccines.

MIS is an inflammatory condition that affects several body user and organs. Manifestations can range from fatigue, high, persistent fever, diarrhoea, vomiting and abdominal pain, to headache, chest pain and difficulty breathing. **MIS has previously been reported in association with COVID-19 infection itself**. *MIS is very rare; based on data from five European studies, its pre-pandemic incidence was estimated to be at around 2 to 6 cases per 100,000 per year in children and adolescents younger than 20 years, to fewer than two cases per 100,000 per year in adults older than 20.*

The PRAC is assessing all available data to seek to establish whether there is a causal link between the occurrence of MIS and the administration of COVID-19 vaccines. EMA and Infarmed will provide information as necessary. It is especially important that all cases of MIS be reported.

COVID-19 Vaccine Janssen®: thromboembolism

Based on data from clinical trials, venous thromboembolism (VTE) has previously been identified as a potential risk associated with this vaccine and has therefore been under close monitoring. In order to assess a possible causal nexus, the PRAC has analyzed the data from two large clinical trials with COVID-19 Vaccine Janssen® as well as data collected during the vaccination campaigns. The conclusion is that there is a reasonable possibility that rare cases of VTE supervene in association with the administration of this vaccine.

The PRAC has thus recommended that VTE should be listed as a rare adverse effect. Healthcare professionals should take this into consideration especially in **persons with increased baseline risk** of thromboembolism.

INDEX CARD

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Vaxzevria® and COVID-19 Vaccine Janssen®: immune thrombocytopenia

Following assessment of cases reported for both these vaccines, the PRAC has recommended listing of immune thrombocytopenia as a possible adverse effect of **unknown frequency**. Cases of very low platelet counts have very rarely been reported usually within the **first four weeks** following vaccination.
This risk should be pondered especially in **persons with a history of immune thrombocytopenia** for whom platelet monitoring should be undertaken following administration of any of the above two vaccines.

Other safety issues

Imbruvica®: concomitant use with rituximab and angiotensin converting enzyme (ACE) inhibitors

Imbruvica® is indicated for the treatment of mantle cell lymphoma, chronic lymphocytic leukaemia (CLL) and Waldenström's macroglobulinaemia (lymphoplasmacytic lymphoma). Its active ingredient is ibrutinib, a potent Bruton tyrosine kinase (BTK) inhibitor, with a limiting effect on the malignant proliferation of B cells.

An interim analysis of the results of a clinical trial has suggested an increased risk of sudden death / sudden cardiac death in patients who were taking ACE inhibitors and who had been randomized into the ibrutinib and rituximab study arm, when compared with patients randomized to receive fludarabine, cyclophosphamide and rituximab.
The PRAC has assessed the emerging data and decided that a review is necessary before further advice can be given to patients and healthcare professionals. While this assessment is ongoing, healthcare professionals should keep using Imbruvica® as per the approved SmPC. Patients should not stop taking ibrutinib or ACE inhibitors without first consulting their doctor.

Medicinal products containing nomegestrol and chlormadinone: risk of meningioma

These medicinal products can be used in isolation or in combination with other active ingredients for the treatment of menstrual disorders and amenorrhoea, uterine bleeding, endometriosis and mastalgia. They can also be used as hormonal replacement therapy or for contraception.

The French medicines agency has requested a safety review following two epidemiological studies in France on the risk of occurrence of meningiomata (tumours of the meninges which are usually not malignant) in women on this type of medication. The PRAC will now undertake an assessment.

Márcia Silva

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

What motivates professionals and patients to report ADRs?

In this study jointly undertaken in Croatia, the Netherlands and the UK, **reasons for reporting** ADRs to the corresponding national medicines agencies were **similar** in these three countries which have in common high baseline reporting rates.

Healthcare professionals and patients were asked to complete an online survey to indicate reasons that would either encourage or discourage them to report ADRs. A total of 296 professionals and 423 patients responded. Consistently across the three countries, most healthcare professionals felt motivated to report when they strongly suspected a causality nexus, when the ADR was serious or was associated with a medicine that had recently been marketed.

Patients on the other hand, and again similarly across the three countries, seem to be mostly driven by seriousness, impact of the ADRs on their daily life activities or by their own personal concerns.

Though not predominant, **differences** were also observed among the countries regarding factors that could either motivate or discourage reporting. In the case of professionals, legal obligation factors were most relevant in Croatia, a black triangle status marking intensive monitoring was given most importance in the UK, whereas whether the ADR was well known was especially relevant in the Netherlands.

On the patient side, Croatian and Dutch patients attached the most importance to a link between their report and its clinical record, while the British gave most weight to reporting complexity and time used, whether the medicine had been purchased on the internet or the ADR was considered embarrassing.

• de Vries ST et al. Motives to Report Adverse Drug Reactions to the National Agency: A Survey Study among Healthcare Professionals and Patients in Croatia, The Netherlands, and the UK. Drug Saf. 2021 Oct;44(10):1073-1083. doi: 10.1007/s40264-021-01098-4. Epub 2021 Aug 8. PMID: 34368940.

Polymedication in mental health conditions: think "natural products" too

This Canadian study (SONAR - Study of Natural Products Adverse Reactions in Adults with Mental Health Conditions) tried to determine the prevalence of adverse effects in adult patients with mental health conditions and who were taking prescription-only medicines, "natural products" or both. An active surveillance methodology was used and applied in eleven mental health clinics in the provinces of Alberta and Ontario.

Of the 3,079 screened patients, 15% reported some adverse effect in the previous thirty days. Over half (59%) occurred in patients who were taking prescription-only medicines and "natural products" simultaneously, 37% in patients who were solely on prescription-only medicines, and 3% in patients taking "natural products" only.

The authors concluded that the combination of the two types of products increases the probability of adverse effects, which is in line with what can be expected from **polymedication in general** and which underscores the relevance of actively monitoring these patients.

• Zorzela L et al. Study of Natural Products Adverse Reactions (SONAR) in Adults with Mental Health Conditions: A Cross-Sectional Study. Drug Saf. 2021 Sep;44(9):999-1006. doi: 10.1007/s40264-021-01092-w. Epub 2021 Jul 28.

Educational Materials published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials? Online publication date
Apixaban *Eliquis*	**Physicians:** cardiology, neurology, internal medicine, general/family medicine, haematology/immuno-haemotherapy, anaesthesiology, orthopaedics, vascular surgery and gastroenterology, clinical directors **Pharmacists:** hospital pharmacy service directors	Prescriber's guide 11-08-2021
Esketamine *Spravato*	**Physicians:** psychiatry **Nurses:** nursing service directors, heads of emergency nursing services **Patients**	Healthcare professional guide Healthcare professional checklist Patient guide 13-08-2021
Natalizumab *Tysabri*	**Physicians:** neurologists treating multiple sclerosis patients **Patients**	Safety information Warning card Start of treatment form Treatment continuation form Treatment suspension form 11-08-2021
Rivaroxaban *Xarelto*	**Physicians:** paediatric cardiology, paediatrics, paediatric oncology, haematology and paediatric surgery	Prescriber's guide 25-08-2021
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Tisagenlecleucel *Kymriah*	**Healthcare professionals:** haematologists, immuno-haemotherapists, paediatric oncologists and intensive care physicians; hospital pharmacists; cryopreservation lab technicians; hospital nurses at qualified centres for this therapy	Training guide for pharmacies, cell labs and perfusion centres 31-08-2021

Compiled by Patrícia Catalão