Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7 - 10 February 2022

News 11/02/2022

PRAC recommends suspending hydroxyethyl-starch solutions for infusion from the market

EMA's safety committee (PRAC) has recommended that marketing authorisations for hydroxyethyl-starch (HES) solutions for infusion should be suspended across the European Union (EU). These products were authorised as an addition to other treatments for plasma volume replacements following acute (sudden) blood loss.

The safety of HES solutions for infusion was reviewed in two separate procedures in 2013, and a number of restrictions and measures to minimise the risk of kidney injury and death in certain patients (those critically ill, with burn injuries or with sepsis, i.e. a bacterial infection in the blood) were put in place at the time.

As a result of a third review conducted in 2018, the use of HES solutions for infusion was further restricted to accredited hospitals, and healthcare professionals prescribing or administering the medicines had to be trained in their appropriate use. Companies marketing HES solutions for infusion were also requested to conduct a drug utilisation study to check that the restrictions were adhered to in clinical practice, and to submit the results of this study to EMA.

The PRAC has now reviewed the results from this study, which show that HES solutions for infusion are still being used outside the recommendations included in the product information. In view of the serious risks that certain patient populations are still exposed to, the PRAC has therefore recommended the suspension of the marketing authorisations for HES solutions for infusion in the EU.

More information is available in EMA's public health communication.

EMA starts safety review of Janus kinase inhibitors for inflammatory disorders

The PRAC has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis).

The review was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). The results showed that patients taking Xeljanz for rheumatoid arthritis and who were at risk of heart disease were more likely to experience a major cardiovascular problem (such as heart attack, stroke or death due to cardiovascular disease) and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors. The study also showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections and blood clots in the lungs and in deep veins (venous thromboembolism VTE).

In addition, preliminary findings from an observational study involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

In the treatment of inflammatory disorders, Olumiant and other JAK inhibitors work in a similar way to Xeljanz. PRAC will therefore carry out a review to determine whether these risks are associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders[1] and whether the marketing authorisations for these medicines should be amended.

Some measures to minimise these risks are already in place for Xeljanz as a result of a review finalised in 2020, which analysed the interim results of study A3921133. In addition, the product information for Xeljanz was further updated in 2021 to reflect the increased risk of major cardiovascular problems and cancer observed after the release of additional data from this study.

More information is available in EMA's public health communication.

PRAC reviewing cases of period irregularities with mRNA COVID-19 vaccines

The PRAC is assessing reported cases of heavy menstrual bleeding (heavy periods) and absence of menstruation (amenorrhea) with the COVID-19 vaccines Comirnaty and Spikevax.

The Committee had previously analysed reports of menstrual (period) disorders in the context of the safety summary reports for COVID-19 vaccines approved in the EU and concluded at the time that the evidence did not support a causal link between these vaccines and menstrual disorders.

In view of spontaneous reports of menstrual disorders with both vaccines and of findings from the literature, the PRAC decided to further assess occurrences of heavy periods or amenorrhea following vaccination.

Menstrual disorders are very common and can occur with a wide range of underlying medical conditions as well as from stress and tiredness. Cases of these disorders have also been reported following COVID-19 infection.

Heavy periods may be defined as bleeding characterised by a volume, which may interfere with the person's physical, social, emotional and material quality of life. Amenorrhea may be defined as the absence of menstrual bleeding for three or more months in a row.

After reviewing the available evidence, the PRAC decided to request an in-depth evaluation of all available data, including reports from spontaneous reporting systems, clinical trials and the published literature.

At this stage, it is not yet clear whether there is a causal link between the COVID-19 vaccines and the reports of heavy periods or amenorrhea. There is also no evidence to suggest that COVID-19 vaccines affect fertility.

EMA will communicate further when more information becomes available.

Updated guidance on core requirements for risk management plans of COVID-19 vaccines

The PRAC has adopted updated guidance on core requirements for risk management plans (RMPs) of COVID-19 vaccines.

As for any medicinal product that is authorised in the EU, companies need to submit their RMP when applying for a marketing authorisation to detail their plan for the post-marketing surveillance and what measures they must put in place to further characterise and manage risks. In the context of the pandemic, EMA adopted specific RMP guidance for COVID-19 vaccines, which complements the existing guidelines on the RMP format in the EU and guidance on good pharmacovigilance practices.

Following discussion at the PRAC, this guidance has been updated in light of the experience accrued during the pandemic to include specific considerations on:

- content requirements for summary safety reports (formerly 'Monthly summary safety reports') to be submitted to EMA by marketing authorisation holders of newly authorised COVID-19 vaccines, and

details on safety topics for which monitoring with the usual periodic safety update reports (PSURs) is more appropriate;
- considerations for summary safety reports' frequency changes and when it is appropriate to remove the requirement to submit such safety reports.

The new version of the guidance is available on EMA's website.

New safety information for healthcare professionals

As part of its advice on safety-related aspects to other EMA committees, the PRAC discussed a direct healthcare professional communication (DHPC) containing important safety information for infliximab.

Advice to postpone use of live vaccines in infants exposed to infliximab during pregnancy or via breastfeeding

This DHPC informs healthcare professionals on the need to postpone the use of live vaccines in infants who are exposed to infliximab during pregnancy or via breastfeeding.

Infliximab is an anti-inflammatory medicine authorised for the treatment of adults with rheumatoid arthritis (an immune system disease causing inflammation of the joints), Crohn's disease (a disease causing inflammation of the digestive tract), ulcerative colitis (a disease causing inflammation and ulcers in the lining of the gut), ankylosing spondylitis (a disease causing inflammation and pain in the joints of the spine), psoriatic arthritis (a disease causing red, scaly patches on the skin and inflammation of the joints) or psoriasis (a disease causing red, scaly patches on the skin). Infliximab is also authorised in patients aged between 6 and 17 years with severe, active Crohn's disease or severely active ulcerative colitis, when they have not responded to or cannot take other medicines or treatments.

Following treatment during pregnancy, it has been reported that infliximab crosses the placenta and it has been detected in infants up to 12 months after birth. Live vaccines should not be given to infants for 12 months after birth if they have been exposed to infliximab during pregnancy. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier time point if there is a clear clinical benefit for the individual infant.

Infliximab has also been detected at low levels in breast milk, therefore, administration of a live vaccine to a breastfed infant while the mother is receiving the medicine is not recommended unless infant infliximab serum levels are undetectable.

It is important that women treated with infliximab who become pregnant or who breastfeed their infant inform the healthcare professional responsible for vaccination of their infant about their treatment with infliximab.

The DHPC for infliximab will be forwarded to EMA's human medicines committee, the CHMP.

Following the CHMP decision, the DHPC will be disseminated to healthcare professionals by the marketing authorisation holders according to an agreed communication plan, and published on the Direct healthcare professional communications page and in national registers in the EU Member States.

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[1] Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib).

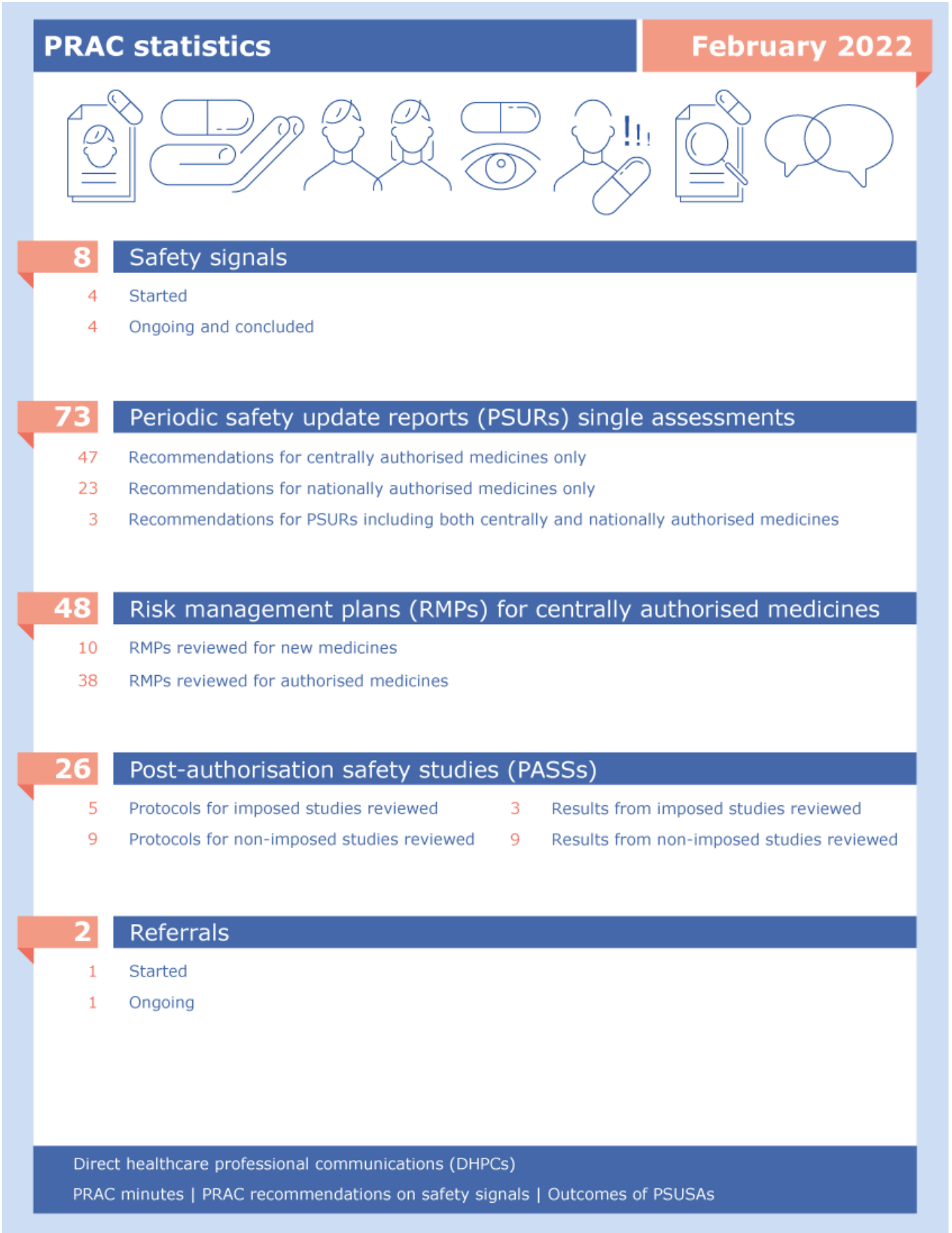
Agenda

Agenda of the PRAC meeting 7-10 February 2022 (PDF/601.84 KB)

Draft

First published: 08/02/2022
EMA/PRAC/76191/2022

PRAC statistics: February 2022



PRAC statistics: February 2022 (PDF/567.47 KB)

First published: 11/02/2022

Glossary:

- **Safety signal assessments**. A safety signal is information which suggests a new potentially causal association, or a new aspect of a known association between a medicine and an adverse event that warrants further investigation. Safety signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. More information can be found under 'Signal management'.
- **Periodic safety update reports**, abbreviated as PSURs, are reports prepared by the marketing authorisation holder to describe the worldwide safety experience with a medicine in a defined period after its authorisation. PSURs for medicinal products that contain the same active substance or the same combination of active substances but have different marketing authorisations and are authorised in different EU Member States, are jointly assessed in a single assessment procedure. More information can be found under 'Periodic safety update reports: questions and answers'.
- **Risk management plans**, abbreviated as RMPs, are detailed descriptions of the activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicines. Companies are required to submit an RMP to EMA when applying for a marketing authorisation. RMPs are continually updated throughout the lifetime of the medicine as new information becomes available. More information is available under 'Risk-management plans'.
- **Post-authorisation safety studies**, abbreviated as PASSs, are studies carried out after a medicine has been authorised to obtain further information on its safety, or to measure the effectiveness of risk-management measures. The PRAC assesses the protocols (aspects related to the organisation of a study) and the results of PASSs. More information can be found under 'Post-authorisation safety studies'.
- **Referrals** are procedures used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral related to safety of medicines, the PRAC is requested by a Member State or the European Commission to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the EU. More information can be found under referral procedures.
- **Summary safety reports** have been introduced as part of the enhanced safety monitoring of COVID-19 vaccines. Marketing authorisation holders are required to submit these reports to EMA, starting on a monthly basis. Their submission complements the submission of PSURs. For more information see EMA's pharmacovigilance plan for COVID-19 vaccines.

Ongoing referrals

Amfepramone-containing medicinal products - Article - 31 Referral
Under evaluation
PRAC continued its assessment.
Nomegestrol and chlormadinone - Article - 31 Referral
Under evaluation
PRAC continued its assessment.
Terlipressin-containing medicinal products-Article 31 Referral
Under evaluation
PRAC continued its assessment.

Related content

- Cibinqo: EPAR
- Comirnaty: EPAR
- Jyseleca: EPAR
- Olumiant: EPAR
- Rinvoq: EPAR
- Spikevax (previously COVID-19 Vaccine Moderna): EPAR
- Comirnaty: Pending EC decision
- Rinvoq: Pending EC decision
- Olumiant: Withdrawn application
- Olumiant: Paediatric investigation plan
- Olumiant: Paediatric investigation plan
- Olumiant: Paediatric investigation plan
- Olumiant: Paediatric investigation plan
- Olumiant: Paediatric investigation plan
- Rinvoq: Paediatric investigation plan
- Rinvoq: Paediatric investigation plan
- Comirnaty: Paediatric investigation plan
- Spikevax (previously COVID-19 Vaccine Moderna): Paediatric investigation plan
- Janus kinase inhibitors (JAKi): Article 20 procedures
- Janus kinase inhibitors (JAKi): Article 20 procedures
- Xeljanz: Article 20 procedures

- PRAC recommends suspending hydroxyethyl-starch solutions for infusion from the market (11/02/2022)
- EMA starts safety review of Janus kinase inhibitors for inflammatory disorders (11/02/2022)
- Safety of COVID-19 vaccines
- COVID-19 vaccines: authorised
- PRAC: Agendas, minutes and highlights
- Pharmacovigilance Risk Assessment Committee (PRAC): 7-10 February 2022

Related documents

Acronyms and abbreviations used in PRAC minutes (PDF/223.84 KB)

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European Union agencies network

An agency of the European Union

Infliximab (Remicade, Flixabi, Inflectra, Remsima and Zessly): Use of live vaccines in infants exposed in utero or during breastfeeding

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About

This direct healthcare professional communication (DHPC) contains important information for healthcare professionals prescribing, dispensing or administering the medicine(s). It also includes a communication plan with details of intended recipients and the dissemination date.

Documents

Direct healthcare professional communication (DHPC): Infliximab (Remicade, Flixabi, Inflectra, Remsima and Zessly): Use of live vaccines in infants exposed in utero or during breastfeeding
(PDF/252.37 KB)

First published: 07/03/2022

Key facts

Medicine name

- Remicade
- Flixabi
- Inflectra
- Remsima
- Zessly

Active substance

infliximab

Therapeutic area (MeSH)

- Spondylitis, Ankylosing
- Arthritis, Rheumatoid
- Psoriasis
- Crohn Disease
- Arthritis, Psoriatic

- Colitis, Ulcerative

Procedure number
EMEA/H/C/000240/IB/233
Regulatory outcome
Variation
DHPC type
New contraindication
Human ATC code
L04AB02
Dissemination date
07/03/2022

Related content

- Remicade
- Flixabi
- Inflectra
- Remsima
- Zessly
- Direct healthcare professional communications

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