27 September 2021[1]
EMA/PRAC/468914/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 30 August-2 September 2021 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 30 August-2 September 2021 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (13-16 September 2021) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the Questions and Answers on signal management.

1. Recommendations for update of the product information[3]

1.1. Methotrexate – Progressive multifocal leukoencephalopathy

Authorisation procedure	Centralised and non-centralised
EPITT No	18473
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	2 September 2021

Recommendation

Taking into consideration the available evidence from published literature, EudraVigilance and data provided by the MAHs, definite causality between methotrexate and PML has not been established, however, a contributory role of methotrexate in development of PML cannot be excluded either.

In order to raise awareness of HCPs and to advise patients accordingly, the PRAC has agreed on the inclusion of a warning in section 4.4 of the SmPC and section 2 of the package leaflet. All MAHs for methotrexate-containing medicinal products should therefore amend the product information as described below.

Summary of product characteristics

4.4. Special warnings and precautions for use

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

Package leaflet

2. What you need to know before you take Methotrexate

If you, your partner or your caregiver notice new onset or worsening of neurological symptoms including general muscle weakness, disturbance of vision, changes in thinking, memory and orientation leading to confusion and personality changes contact your doctor immediately because these may be symptoms of a very rare, serious brain infection called progressive multifocal leukoencephalopathy (PML).

[3] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

1.2. Ponatinib – Panniculitis

Authorisation procedure	Centralised
EPITT No	19681
PRAC rapporteur(s)	Annika Folin (SE)
Date of adoption	2 September 2021

Recommendation

Having considered the available evidence and following the assessment of the data submitted by the concerned Marketing Authorisation Holder (MAH), the PRAC has agreed that the product information for ponatinib should be updated to reflect the risk of panniculitis.

The MAH of Iclusig (Incyte Biosciences Distribution B.V.), should submit a variation within two months from the publication of the PRAC recommendation, to amend the product's information as described here (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Table 4

System Organ Class - Skin and subcutaneous tissue disorders

Rare: panniculitis (including erythema nodosum)

Package leaflet

4. Possible side effects

Other possible side effects that may occur with the following frequencies are:

Rare (may affect up to 1 in 1,000 people)

- Painful red lumps, skin pain, skin reddening (inflammation of fatty tissue under the skin)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Alemtuzumab	Autoimmune encephalitis (19710)	Anette Kirstine Stark (DK)	Assess in the next PSUR (submission by 21 November 2021)	Sanofi Belgium
COVID-19 mRNA[4] vaccine (nucleoside-modified) – Comirnaty	Multisystem inflammatory syndrome (19732)	Menno van der Elst (NL)	Supplementary information requested (submission by 24 September 2021)	BioNTech Manufacturing GmbH
COVID-19 mRNA[5] vaccine (nucleoside-modified) – Spikevax	Multisystem inflammatory syndrome (19732)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 24 September 2021)	Moderna Biotech Spain, S.L.
COVID-19 vaccine (Ad26.COV2-S [recombinant]) - COVID-19 Vaccine Janssen	Multisystem inflammatory syndrome (19732)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 24 September 2021)	Janssen-Cilag International NV
COVID-19 vaccine (ChAdOx1-S [recombinant]) – Vaxzevria	Multisystem inflammatory syndrome (19732)	Jean-Michel Dogné (BE)	Supplementary information requested (submission by 24 September 2021)	AstraZeneca AB
Durvalumab	Arthralgia (19709)	David Benee Olsen (NO)	Supplementary information requested (submission by 3 November 2021)	AstraZeneca AB
Obinutuzumab	Non-overt disseminated intravascular coagulation (DIC) (19711)	Annika Folin (SE)	Supplementary information requested (submission by 3 November 2021)	Roche Registration GmbH
Pregabalin	Toxic epidermal necrolysis (19723)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 3 November 2021)	Upjohn EESV

[4] Messenger ribonucleic acid
[5] Messenger ribonucleic acid

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Tocilizumab	Sarcoidosis (18860)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 3 November 2021)	Roche Registration GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Fluoroquinolones: ciprofloxacin; delafloxacin; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Acquired thrombotic thrombocytopenia purpura (19669)	Pernille Harg (NO)	Routine pharmacovigilance	MAHs of fluoroquinolones
Ibrutinib	Sudden death/cardiac death with ibrutinib and concomitant angiotensin-converting enzyme (ACE) inhibitors from a clinical trial (19726)	Nikica Mirošević Skvrce (HR)	No action at this stage	Janssen-Cilag International
COVID-19 vaccine (ChAdOx1-S [recombinant]) – Vaxzevria	Capillary leak syndrome (19672)	Jean-Michel Dogné (BE)	Monitor within the monthly summary safety reports (MSSRs) and periodic safety update reports (PSURs)	AstraZeneca AB
COVID-19 mRNA[6] vaccine (nucleoside-modified) – Comirnaty	Myocarditis and pericarditis (19712)	Menno van der Elst (NL)	Monitor within the monthly summary safety reports (MSSRs)	BioNTech Manufacturing GmbH
COVID-19 mRNA[7] vaccine (nucleoside-modified) - Spikevax	Myocarditis and pericarditis (19713)	Hans Christian Siersted (DK)	Monitor within the monthly summary safety reports (MSSRs)	Moderna Biotech Spain, S.L.

[6] Messenger ribonucleic acid
[7] Messenger ribonucleic acid