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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 6-9 July 2020 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 6-9 July 2020 (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 (20-23 July 2020) 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.

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.

[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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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. Lisdexamfetamine – QT prolongation and cardiac arrhythmia

Authorisation procedure	Non-centralised
EPITT No	19533
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	9 July 2020

Recommendation *[see also section 3]*

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 lisdexamfetamine should be updated to reflect the risk of QTc prolongation.

The MAHs of lisdexamfetamine containing products should submit a variation within two months from the publication of the PRAC recommendation, to amend the product information as described here (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Cardiovascular adverse events

Hypertension and other cardiovascular conditions

Lisdexamfetamine has shown to prolong the QTc interval in some patients. It should be used with caution in patients with prolongation of the QTc interval, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

4.8. Undesirable effects

Tabulated list of adverse reactions

Cardiac disorders

Adverse Reaction: QTc prolongation; Frequency not known (*for all age categories*)

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2. What you need to know before you take <product name>

Warnings and precautions

Talk to your doctor or pharmacist before using <product name> treatment if you have:

- family or medical history of irregular heart rhythm (visible on an electrocardiogram), or if you have a disease and/or take a treatment that make(s) you prone to heartbeat irregularities or salt imbalances

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

Tell your doctor or pharmacist if any of the above applies to you before starting treatment. This is because <product name> can make these problems worse. Your doctor will want to monitor how the medicine affects you.

<Product name> may cause heart rhythm disorders in some patients. If you experience palpitations or irregular heartbeat during the period of treatment, you should inform your doctor immediately. The risk of heart problems may increase with increase of the dose. Therefore, the recommended dosage should be followed.

4. Possible side effects

Some side effects could be serious. If you get any of the side effects below, see a doctor straight away:

Not known: frequency cannot be estimated from the available data

- Abnormal heart rhythm, life-threatening irregular heart rhythm (seen on an electrocardiogram). See section 2, Warnings and precautions.

1.2. Tumour necrosis factor alpha inhibitors: adalimumab; certolizumab pegol; etanercept; golimumab; infliximab – Kaposi's sarcoma

Authorisation procedure	Centralised
EPITT No	19480
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	9 July 2020

Recommendation

Having considered the reviews of the data submitted and the comments received, the PRAC has concluded that the product information of all medicinal products containing an anti-TNF agent (i.e. adalimumab, certolizumab, etanercept, golimumab and infliximab) should be updated with the Kaposi's sarcoma term. The MAHs of all medicinal products containing an anti-TNF agent (both innovator and biosimilar) should submit a variation within 2 months from the publication of the PRAC recommendation to update the ADR table of the section 4.8 (SOC Neoplasms) of the SmPC with Kaposi's sarcoma, with frequency unknown. The corresponding section 4 of the PL should be updated accordingly.

For the respective products, the following changes and proposed additions in the SmPCs / PLs are presented below with new text underlined.

- **Humira (adalimumab)**

Summary of product characteristics

4.8. Undesirable effects

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Not known: Hepatosplenic T-cell lymphoma1), Merkel cell carcinoma (neuroendocrine carcinoma of the skin), Kaposi's sarcoma

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4. Possible side effects

Not known (frequency cannot be estimated from available data)

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

• Cimzia (certolizumab)

Summary of product characteristics

4.8. Undesirable effects

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Not known: Merkel cell carcinoma*, Kaposi's sarcoma

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4. Possible side effects

Not known (frequency cannot be estimated from the available data):

- multiple sclerosis*
- Guillain-Barré syndrome*
- Merkel cell carcinoma (a type of skin cancer)*
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.

• Enbrel (etanercept)

Summary of product characteristics

4.8. Undesirable effects

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Frequency not known (cannot be estimated from available data):

Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma

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4. Possible side effects

Not known (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi's sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

• Simponi (golimumab)

Summary of product characteristics

4.8. Undesirable effects

Neoplasms, benign, malignant and unspecified

Not known: Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma

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4. Possible side effects

Side effects of which the frequency is not known:

- A rare blood cancer affecting mostly young people (hepatosplenic T-cell lymphoma)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.

• Remicade (infliximab)

Summary of product characteristics

4.8. Undesirable effects

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Rare: Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer.
Not known: Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease or ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma

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4. Possible side effects

Not known (frequency cannot be estimated from the available data)

- Cancer in children and adults
- A rare blood cancer affecting mostly teenage boys or young men (hepatosplenic T-cell lymphoma)
- Liver failure

- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Heart attack
- Stroke
- Temporary loss of sight during or within 2 hours of infusion
- Infection due to a live vaccine because of a weakened immune system

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Abnormal weight gain (19520)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 26 August 2020)	AbbVie Deutschland GmbH & Co.
Anakinra; canakinumab	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19566)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 26 August 2020)	Swedish Orphan Biovitrum AB, Novartis Europharm Limited
Dabrafenib; trametinib	Sarcoidosis (19574)	David Olsen (NO)	Supplementary information requested (submission by 26 August 2020)	Novartis Europharm Limited
Ibrutinib	Hepatitis E (19569)	Nikica Mirošević Skvrce (HR)	Supplementary information requested (submission by 26 August 2020)	Janssen-Cilag International NV
Palbociclib	Cutaneous lupus erythematosus (19571)	Hans Christian Siersted (DK)	Assess in the next PSUR (submission by 11 October 2020)	Pfizer Europe MA EEIG
Teriparatide	Myeloma (19511)	Adrien Inoubli (FR)	Supplementary information requested (submission by 26 August 2020)	Eli Lilly, Teva, Stada, Gedeon Richter

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Lisdexamfetamine	QT prolongation and cardiac arrhythmia (19533)	Ulla Wändel Liminga (SE)	· See section 1.1 · Monitor in PSURs the risk of arrhythmias, cardiac arrest and sudden death	MAHs of lisdexamfetamine-containing products
Lopinavir, ritonavir	Adrenal dysfunction in infants (19527)	Adrien Inoubli (FR)	Routine pharmacovigilance	MAHs of lopinavir/ritonavir-containing products