22 October 2015
EMA/PRAC/661789/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 5-8 October 2015

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 5-8 October 2015 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] 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 (19-22 October 2015) 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] 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[2]

1.1. Anakinra – Thrombocytopenia

Authorisation procedure	Centralised
EPITT No	18337
PRAC rapporteur(s)	Torbjörn Callreus (DK)
Date of adoption	8 October 2015

Recommendation

Having considered the available evidence in EudraVigilance and the literature, the data submitted by the MAH, as well as a plausible mechanism associated with the inhibition of interleukin 1ß (IL-1ß) by anakinra, the PRAC has agreed that the MAH of Kineret (Swedish Orphan Biovitrum AB) should submit a variation within 2 months, to amend the product information as described below (new text underlined).

Summary of Product Characteristics:

Section 4.8 – Undesirable effects:

Blood and lymphatic system disorders

Frequency 'common': thrombocytopenia

Thrombocytopenia

In clinical studies in RA and CAPS patients, thrombocytopenia has been reported in 1.9% of treated patients compared to 0.3% in the placebo group. The thrombocytopenias have been mild, i.e. platelet counts have been >75 $x10^9$/l.

During post-marketing use of Kineret, thrombocytopenia has been reported, including occasional case reports indicating severe thrombocytopenia (i.e. platelet counts <10 $x10^9$/l).

Package Leaflet:

4. Possible side effects

Common side effects (may affect up to 1 in 10 people):

- Thrombocytopenia (low level of blood platelets).

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

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Autoimmune haemolytic anaemia (AIHA) and haemolytic anaemia (HA) (18447)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 09/12/2015)	AbbVie Ltd
Alogliptin; Linagliptin	Arthralgia (18489)	Menno van der Elst (NL)	Supplementary information requested (submission by 09/12/2015)	Takeda Pharma A/S; Boehringer Ingelheim International GmbH
Carbidopa, levodopa	Intussusception (18424)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 09/12/2015)	AbbVie Ltd
Ibrutinib	Peripheral neuropathy (18480)	Julie Williams (UK)	Assess in the next PSUR (submission by 21/01/2016)	Janssen-Cilag International NV
Mitotane	Sex hormone disturbances and development of ovarian macrocysts (18301)	Dolores Montero Corominas (ES)	Supplementary information requested (submission by 09/12/2015)	Laboratoire HRA Pharma, SA
Peginterferon alfa-2a	Acquired haemophilia (18476)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 09/12/2015)	Roche Registration Limited
Ustekinumab	Pemphigoid (18469)	Julie Williams (UK)	Supplementary information requested (submission by 09/12/2015)	Janssen-Cilag International N.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Convulsion (18211)	Ulla Wändel Liminga (SE)	No action	AbbVie Ltd
Boceprevir	Hyponatraemia (18350)	Isabelle Robine (FR)	Monitor in PSUR	Merck Sharp & Dohme Limited
Fluoroquinolones: ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Retinal detachment (15914)	Valerie Strassmann (DE)	No action at this stage	Not applicable
Sitagliptin	Intestinal obstruction (18251)	Menno van der Elst (NL)	Monitor in PSUR	Merck Sharp & Dohme Limited