6 August 2018[1]
EMA/PRAC/414645/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 9-12 July 2018 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 9-12 July 2018 (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 (23-26 July 2018) 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] Intended 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. Antiretrovirals – Autoimmune hepatitis*

Authorisation procedure	Centralised and non-centralised
EPITT No	18956
PRAC rapporteur(s)	Ana Sofia Diniz Martins (PT)
Date of adoption	12 July 2018

* List of antiretrovirals: abacavir; abacavir, dolutegravir, lamivudine; abacavir; abacavir, lamivudine, zidovudine; atazanavir; atazanavir, cobicistat; bictegravir, emtricitabine, tenofovir alafenamide; darunavir; darunavir, cobicistat; darunavir, cobicistat, emtricitabine, tenofovir alafenamide; didanosine; dolutegravir; dolutegravir, rilpivirine; efavirenz ; efavirenz, emtricitabine, tenofovir disoproxil; elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide; elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil; emtricitabine; emtricitabine, rilpivirine, tenofovir alafenamide; emtricitabine, rilpivirine, tenofovir disoproxil; emtricitabine, tenofovir alafenamide; emtricitabine, tenofovir disoproxil; enfuvirtide; etravirine; fosamprenavir; indinavir; lamivudine; lamivudine, tenofovir; lamivudine, zidovudine; lopinavir, ritonavir; maraviroc; nevirapine; raltegravir; rilpivirine; ritonavir; saquinavir; stavudine; tenofovir disoproxil; tipranavir; zidovudine

Recommendation

Having considered the evidence from EudraVigilance and the literature, and the responses from the MAHs, the PRAC has agreed that the MAHs of antiretroviral medicinal products against HIV should submit a variation within 3 months, to amend the Summary of Product Characteristics as described below (new text underlined). No changes to the package leaflet are considered necessary as symptoms associated with hepatitis are already described.

Summary of product characteristics

4.4. Special warnings and precautions for use

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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

4.8. Undesirable effects

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

1.2. Human normal immunoglobulin for intravenous administration (IVIg) – Lupus-like syndrome and related terms

Authorisation procedure	Centralised and non-centralised
EPITT No	19098
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	12 July 2018

Recommendation *[see also section 3]*

Having considered the available evidence, including the views of the Blood Product Working Party (BPWP) on lupus like syndrome and related terms (cutaneous lupus erythematosus) as well as the data submitted by the concerned companies, the PRAC has agreed that the MAHs of intravenous Normal Human Immunoglobulin (IvIgs) containing medical products should submit a variation within 3 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown) have been observed with human normal immunoglobulin.

Packet leaflet

4. Possible side effects

Section 4 of the package leaflet does not need to be updated since clinical symptoms of cutaneous lupus erythematosus are already captured.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Certolizumab pegol; etanercept; golimumab; infliximab	Lichenoid skin reactions (19128)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 26 September 2018)	UCB Pharma SA, Pfizer Limited, Janssen Biologics B.V.
Dasabuvir; ombitasvir, paritaprevir, ritonavir	Interstitial lung disease (19257)	Dolores Montero Corominas (ES)	Supplementary information requested (submission by 26 September 2018)	AbbVie Deutschland GmbH & Co. KG
Montelukast	Dysphemia (speech disorders) (19275)	Kimmo Jaakkola (FI)	Assess in the next PSUR (submission by 28 October 2018)	Merck Sharp & Dohme
Olmesartan	Autoimmune hepatitis (19258)	Martin Huber (DE)	Supplementary information requested (submission by 26 September 2018)	Originators MAH for olmesartan-containing medicinal products
Pembrolizumab	Systemic inflammatory response syndrome (SIRS) (19267)	Sabine Straus (NL)	Assess in the next PSUR (submission by 12 November 2018)	Merck Sharp & Dohme B.V.
Perindopril	Raynaud's phenomenon (19248)	Doris Stenver (DK)	Supplementary information requested (submission by 26 September 2018)	Laboratoires Servier
Propranolol	Increased risk of Parkinson's disease (19223)	Pernille Harg (NO)	Supplementary information requested (submission by 26 September 2018)	AstraZeneca AB
Ranibizumab	Angioedema (19245)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 26 September 2018)	Novartis Europharm Limited
Thiamazole; carbimazole	Pancreatitis (19274)	Martin Huber (DE)	Supplementary information requested (submission by 26 September 2018)	MAHs for the innovator of the medicinal products containing

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
				thiamazole or carbimazole; MAHs for thiamazole or carbimazole belonging to Novartis
Vemurafenib	Cardiac failure (19268)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 26 September 2018)	Roche Registration GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amitriptyline; dosulepin; oxybutynin; paroxetine; procyclidine; tolterodine	Dementia (19263)	Laurence de Fays (BE)	Monitor in PSUR	MAHs of oxybutynin, tolterodine, amitriptyline, paroxetine, dosulepin and procyclidine containing products
Fluoroquinolones (for systemic use): ciprofloxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Aortic aneurysm and dissection (18651)	Martin Huber (DE)	Provide comments on proposed updates to the product information (submission by 13 August 2018)	Angelini, Bayer, Biocodex, Grünenthal, Laboratoires Gerda, Mediolanum, Sanofi, Vianex

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Hormonal contraceptives	Known association between hormonal contraceptives and a small increase in breast cancer following a recent publication (19143)	Menno van der Elst (NL)	Provide proposal for product information updates (submission by 1 August 2018)	Innovator MAHs for the combined hormonal contraceptive products; MAHs for LNG-IUS products
Human normal immunoglobulin	Lupus-like syndrome and related terms (19098)	Brigitte Keller-Stanislawski (DE)	· See section 1.2 · Monitor in PSUR	MAHs of intravenous normal human immunoglobulin containing products
Hydrochlorothiazide	Skin cancer (19138)	Kirsti Villikka (FI)	Provide comments on proposed updates to the product information; propose a communication plan and a Direct Healthcare Professional Communication (DHPC) (submission by 3 August 2018)	Innovator MAHs for hydrochlorothiazide containing products
Levothyroxine; ombitasvir, paritaprevir, ritonavir	Interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism (18896)	Menno van der Elst (NL)	No action for MAH (no product information update warranted for Viekirax to reflect the interaction between levothyroxine and ritonavir)[4]	AbbVie Deutschland GmbH & Co. KG

[4] The document summarising the PRAC recommendations on signals adopted at the 5-8 February 2018 PRAC meeting has been amended accordingly.