23 March 2017
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 6-9 March 2017 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 March 2017 (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 (20-23 March 2017) 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. Loperamide – Serious cardiac events with high doses of loperamide from abuse and misuse

Authorisation procedure	Non-centralised
EPITT No	18339
PRAC rapporteur(s)	Andri Andreou (CY)
Date of adoption	9 March 2017

Recommendation *[see also section 3]*

Having considered the available evidence from spontaneous reporting and in the literature, the PRAC has agreed that the MAHs of loperamide-containing medicinal products should submit a variation within 2 months, to amend the product information as applicable (taking into account the already existing wording in some nationally authorised products), in order to include the text as described below:

Summary of product characteristics

4.4. Special warnings and precautions for use

Cardiac events including QT prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

4.9. Overdose

In individuals who have ingested overdoses of loperamide HCl, cardiac events such as QT interval prolongation, torsades de pointes, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed (see section 4.4). Fatal cases have also been reported.

5.3. Preclinical safety data

Non-clinical in vitro and in vivo evaluation of loperamide indicates no significant cardiac electrophysiological effects within its therapeutically relevant concentration range and at significant multiples of this range (up to 47-fold). However, at extremely high concentrations associated with overdoses (see section 4.4), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

Package leaflet

2 - What you need to know before you take <brand name>

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

Warnings and precautions

Do not take this product for anything other than its intended use (see section 1) and never take more than the recommended amount (see section 3). Serious heart problems (symptoms of which include fast or irregular heartbeat) have been reported in patients who have taken too much loperamide, the active ingredient in <brand name>.

3 - If you take more <brand name> than you should

If you have taken too many <brand name>, immediately contact a doctor or hospital for advice. Symptoms may include: increased heart rate, irregular heartbeat, changes to your heartbeat (these symptoms can have potentially serious, life-threatening consequences), muscle stiffness, uncoordinated movements, drowsiness, difficulty urinating, or weak breathing.

Children react more strongly to large amounts of <brand name> than adults. If a child takes too much or shows any of the above symptoms, call a doctor immediately.

1.2. Nivolumab; pembrolizumab – Transplant rejection

Authorisation procedure	Centralised
EPITT No	18781
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	9 March 2017

Recommendation *[see also section 3]*

Having considered the available evidence from case reports in EudraVigilance and in the literature, as well as the biological plausibility from its mechanism of action, the PRAC has agreed that the MAHs of Opdivo (Bristol-Myers Squibb) and of Keytruda (Merck Sharp & Dohme) should, respectively for their own product, submit a variation within 2 months to amend the summary of product characteristics and package leaflet as described below (new text underlined, text to be removed with ~~strikethrough~~) […]:

Opdivo (nivolumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Other immune-related adverse reactions

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

4.8. Undesirable effects

Immune system disorders

Nivolumab monotherapy

Frequency ‘not known’: Solid organ transplant rejection

Nivolumab in combination with ipilimumab

Frequency ‘not known’: Solid organ transplant rejection

Package leaflet

2 - What you need to know before you use OPDIVO

Warnings and precautions

Talk to your doctor before using OPDIVO as it may cause:

Solid organ transplant rejection

Keytruda (pembrolizumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Other immune-related adverse reactions

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with pembrolizumab versus the risk of possible organ rejection should be considered in these patients.

4.8. Undesirable effects

Immune system disorders

Frequency ‘not known’: Solid organ transplant rejection

Package leaflet

2 - What you need to know before you are given KEYTRUDA

Warnings and precautions

Before you get KEYTRUDA, tell your doctor if you:

- have liver damage ~~or have had a liver transplant~~

- have kidney damage ~~or have had a kidney transplant~~

- have a solid organ transplant

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Enzalutamide	Hepatotoxicity (18754)	Eva Segovia (ES)	Supplementary information requested (submission by 3 May 2017)	Astellas Pharma Europe B.V.
Fulvestrant	Anaphylactic reaction (18832)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 3 May 2017)	AstraZeneca UK Ltd
Meropenem; ciprofloxacin	Incompatibility leading to possible precipitation when co-administered intravenously (18790)	Jan Neuhauser (AT)	Supplementary information requested (submission by 3 May 2017)	AstraZeneca; Bayer

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Docetaxel	Unexpected seriousness of the reported adverse drug reactions (ADR) and suspicion of an increase in the ADR reporting rate in France (12059)	Claire Férard (FR)	No action at this stage	Not applicable
Loperamide	Serious cardiac events with high doses of loperamide from abuse and misuse (18339)	Andri Andreou (CY)	· See section 1.1 · Update the RMP · Monitor in the PSUR (QT prolongation and/ or serious ventricular arrhythmias including torsades de pointes) · Next PSUR submission DLP is moved to 31/05/2018 and continuing with a 3-yearly cycle thereafter	MAHs of loperamide-containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Nivolumab; pembrolizumab	Transplant rejection (18781)	Brigitte Keller-Stanislawski (DE)	· See section 1.2 · Update the RMP	Bristol-Myers Squibb Pharma EEIG; Merck Sharp & Dohme Limited