14 December 2017
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 27-30 November 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 27-30 November 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 (11-14 December 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. Insulin (pre-filled pens and cartridges): insulin aspart; insulin bovine; insulin degludec; insulin degludec, insulin aspart; insulin degludec, liraglutide; insulin detemir; insulin glargine; insulin glulisine; insulin human (rDNA); insulin human, insulin isophane; insulin lispro; insulin porcine – Potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia

Authorisation procedure	Centralised and non-centralised
EPITT No	18893
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	30 November 2017

Recommendation

Having considered the available evidence, including the views of the Health Care Professional (HCP) experts on medication errors and diabetes and of patients and the data submitted by the MAHs, the PRAC has agreed the following recommendation:

1. High-strength and fixed-combination insulin products

For these products the PRAC has already made recommendations published on 29 May 2017. No further action is required.

2. Standard (100 units/mL) and lower (< 100 units/mL) strength insulin products

The MAH(s) of standard or low strength insulin-containing medicinal products in cartridges (for use with reusable pens) and pre-filled pens should submit a variation within 2 months, to amend the product information as described below (new text to be added underlined, text to be adapted by MAHs to individual products **in bold**):

Summary of product characteristics (SmPC)

6.6. Special precautions for disposal and other handling

The following text and any related package leaflet text should be removed: 'If the <pen / infusion pump> malfunctions (see instructions for using the pen / infusion pump), the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 units/mL) and injected.'

4.2. Posology and method of administration, and/or 4.4. Special warnings and precautions for use

<<Product name in cartridges> is only suitable for subcutaneous injections from a reusable pen.

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

< If administration by syringe, <intravenous injection> or <infusion pump> is necessary, a vial should be used.>>

<<Product name in pre-filled pen> is only suitable for subcutaneous injections.

<If administration by syringe, <intravenous injection> or <infusion pump> is necessary, a vial should be used.>>

Package leaflet (PL)

2. What you need to know before you use <product name>, and 3. How to use <product name>

<Product name in cartridges> is only suitable for injecting just under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.

<Product name in pre-filled pen> is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

3. 'Umbrella' product information

Summary of product characteristics

'Umbrella' SmPCs (for different presentations of the same product) should make it clear that administration by syringe and/or other devices (and different routes of administration) do not apply to use with pre-filled pens/cartridges for reusable pens. The layout/order of text as well as the actual language used should be reviewed and amended as necessary.

In addition, PRAC agreed that the references to different routes of administration (e.g. intravenous use, infusion pumps) that are inappropriate for use with pre-filled pens/cartridges for reusable pens, should be deleted from individual SmPCs and PLs.

PRAC has also agreed key messages for communication to HCP and patients at the national level.

1.2. Tofacitinib – Angioedema

Authorisation procedure	Centralised
EPITT No	18904
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	30 November 2017

Recommendation

Having considered the available evidence in EudraVigilance and the data submitted by the MAH on the association of tofacitinib and angioedema, the PRAC has agreed that the MAH of Xeljanz (Pfizer) should submit a variation within 2 months to amend the product information as described below (new text underlined).

Summary of product characteristics

4.4. Special warnings and precautions for use

Hypersensitivity

In post-marketing experience, cases of hypersensitivity associated with tofacitinib administration have been reported. Allergic reactions included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, tofacitinib should be discontinued immediately.

4.8. Undesirable effects

Immune system disorders

Frequency 'not known': hypersensitivity; angioedema; urticaria

Package leaflet

4. Possible side effects

Other side effects which have been observed with XELJANZ are listed below.

Not known (frequency cannot be estimated from the available data): hives (itchy, bumpy rash)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Daratumumab	Cytomegalovirus (CMV) reactivation (19087)	Márcia Sofia Silva (PT)	Assess in the next PSUR (submission by 24 January 2018)	Janssen-Cilag International NV
Dasatinib	Cytomegalovirus (CMV) reactivation (19111)	Doris I Stenver (DK)	Supplementary information requested (submission by 7 February 2018)	Bristol-Myers Squibb Pharma EEIG
Human normal immunoglobulin	Lupus-like syndrome and related terms (19098)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 February 2018)	MAHs of Human normal immunoglobulin -containing products
Lapatinib	Pulmonary hypertension (19089)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 7 February 2018)	Novartis Europharm Limited
Vortioxetine	Angioedema (19099)	Laurence de Fays (BE)	Supplementary information requested (submission by 7 February 2018)	H. Lundbeck A/S

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
mTOR inhibitors: everolimus, sirolimus, temsirolimus	Optic neuropathy and papilloedema (18901)	Martin Huber (DE)	Routine pharmacovigilance	Novartis Europharm Ltd, Pfizer Limited
Nivolumab	Tumour lysis syndrome (19086)	Brigitte Keller-Stanislawski (DE)	To be addressed within the ongoing PSUR procedure (EMEA/H/C/PSUSA/00010379/201707)	Bristol-Myers Squibb Pharma EEIG
Phenprocoumon	Risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal (18902)	Martin Huber (DE)	Propose an updated product information (submission by 7 February 2018)	MEDA Pharma GmbH & Co. KG
Radium (^{223}Ra) dichloride	Fractures and fatal cases in chemotherapy-naïve patients (19132)	Patrick Batty (UK)	Circulation of a Direct Healthcare Professional Communication (DHPC); further action to be addressed within the procedure under Article 20 of Regulation (EC) No 726/2004 for radium (^{223}Ra) dichloride	Bayer AG
Ritonavir; lopinavir, ritonavir; levothyroxine	Interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism (18896)	Menno van der Elst (NL)	No action at this stage	Not applicable