26 May 2016
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 10-13 May 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 10-13 May 2016 (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 (23-26 May 2016) 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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. Natalizumab – Necrotising retinitis

Authorisation procedure	Centralised
EPITT No	18605
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	13 May 2016

Recommendation

Having considered the available evidence, the PRAC has agreed that the MAH for Tysabri (natalizumab) should submit a variation within 2 months, to amend the product information (PI) as described below (new text underlined). The MAH should update the relevant sections of the Risk Management Plan to include acute retinal necrosis under Herpes infections. Communication of the update of the PI should be agreed on the national basis.

Summary of Product Characteristics

Section 4.4 - Special warnings and precautions for use

Infections including other opportunistic infections

[…] If herpes encephalitis or meningitis occurs, TYSABRI should be discontinued and appropriate treatment for herpes encephalitis or meningitis should be administered.

Acute retinal necrosis (ARN) is a rare fulminant viral infection of the retina caused by the family of herpes viruses (e.g. varicella zoster). ARN has been observed in patients being administered TYSABRI and can be potentially blinding. Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, discontinuation of TYSABRI should be considered in these patients.

Section 4.8 - Undesirable effects

Infections, including PML and opportunistic infections

[…] The duration of treatment with TYSABRI prior to onset ranged from a few months to several years (see section 4.4).

In post-marketing experience, rare cases of acute retinal necrosis (ARN) have been observed in patients receiving TYSABRI. Some cases have occurred in patients with central nervous system (CNS) herpes infections (e.g. herpes meningitis and encephalitis). Serious cases of ARN, either affecting one or both eyes, led to blindness in some patients. The treatment reported in these cases included anti-viral therapy and in some cases, surgery (see section 4.4).

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

Package Leaflet

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Speak to your doctor or nurse immediately if you notice any of the following

Symptoms of serious infections including:

- An unexplained fever
- Severe diarrhoea

[…]

- Impaired vision
- Pain or redness of the eye(s)

1.2. Warfarin – Calciphylaxis

Authorisation procedure	Non-centralised
EPITT No	18545
PRAC rapporteur(s)	Torbjörn Callreus (DK)
Date of adoption	13 May 2016

Recommendation

Having considered the available evidence from EudraVigilance, the literature, the analysis submitted by Takeda and Bristol-Myers Squibb, as well as the existence of a plausible biological mechanism, the PRAC has concluded that there is a reasonable possibility of a causal relationship between calciphylaxis and the use of warfarin. The PRAC has agreed that the MAH(s) of warfarin-containing medicinal products should submit a variation within 3 months, to amend the product information as described below (new text underlined):

Summary of Product Characteristics

Section 4.4 - Special warnings and precautions for use

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

Section 4.8 - Undesirable effects

Skin and subcutaneous tissue disorders

Frequency ‘not known’: Calciphylaxis

Package Leaflet:

4. Possible side effects

Tell your doctor straight away if you have any of the following side effects…:

[…]

A painful skin rash. On rare occasions warfarin can cause serious skin conditions, including one called calciphylaxis that can start with a painful skin rash but can lead to other serious complications. This adverse reaction occurs more frequently in patients with chronic kidney disease.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Anakinra; canakinumab	Weight increased (18641)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 27 July 2016)	Swedish Orphan Biovitrum AB (publ); Novartis Europharm Ltd
Dexlansoprazole; lansoprazole	Unexpected histopathological findings from a juvenile rat toxicity study (18645)	Kirsti Villikka (FI)	Supplementary information requested (submission by 27 July 2016)	Takeda
Fluconazole	Spontaneous abortion during pregnancy and stillbirth (18666)	Doris I. Stenver (DK)	Supplementary information requested (submission by 27 July 2016)	Pfizer
Fluoroquinolones (for systemic use): ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Aortic aneurysm and dissection (18651)	Valerie Strassmann (DE)	Supplementary information requested (submission by 27 July 2016)	Angelini; Bayer; Delta; Gerda; Mediolanum; MSD; Pierre Fabre; Rottapharm; Sanofi-Aventis

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Levetiracetam (oral solution)	Medication errors associated with accidental overdoses (10519)	Veerle Verlinden (BE)	Supplementary information requested (submission by 24 August 2016)	UCB Pharma S.A.
Metronidazole	Severe hepatic and neurologic toxicity in patients with Cockayne syndrome (18663)	Martin Huber (DE)	Supplementary information requested (submission by 27 July 2016)	Sanofi-Aventis; Dr. August Wolff
Quinine	Increased mortality risk in heart failure patients with/without concomitant use of beta-blockers (18529)	Almath Spooner (IE)	Assess in the next PSUR (submission as per EURD list)	Actavis UK Ltd; Alept; Artecef BV; Athlone Laboratories Ltd; Bristol Laboratories Ltd; Casella-Med Gmbh & Co.KG; Dalkeith Laboratories Ltd; Laboratoire Innotech International
Regorafenib	Angioedema (18656)	Sabine Straus (NL)	Supplementary information requested (submission by 27 July 2016)	Bayer Pharma AG
Vedolizumab	Hepatotoxicity (18646)	Adam Przybylkowski (PL)	Assess in the ongoing PSUSA procedure EMEA/H/C/PSUSA/00010186/201511	Takeda Pharma A/S

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Glomerulonephritis (18528)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	AbbVie Ltd
Clozapine	Myocarditis (18414)	Julie Williams (UK)	Routine pharmacovigilance	MAHs of clozapine containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cytarabine	Benign intracranial hypertension (18533)	Rafe Suvarna (UK)	Routine pharmacovigilance	Pacira Ltd
Dapagliflozin; dapagliflozin, metformin	Pancreatitis (18558)	Qun-Ying Yue (SE)	Monitor in PSUR	AstraZeneca AB
Fluoroquinolones (for systemic use): ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Retinal detachment (15914)	Valerie Strassmann (DE)	Routine pharmacovigilance	MAHs of fluoroquinolone-containing medicinal products for systemic use
Gefitinib	Pneumatosis intestinalis (18575)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	AstraZeneca AB
Infliximab	Thyroid gland disorders (18530)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	Janssen Biologics B.V.
Methotrexate	Congenital cardiovascular anomaly (18481)	Doris I. Stenver (DK)	Routine pharmacovigilance	MAHs of methotrexate containing products
Selective serotonin reuptake inhibitors (SSRIs): citalopram; escitalopram; fluoxetine; fluvoxamine; mirtazapine; paroxetine; sertraline; and	Risk of autism spectrum disorders (ASD) after maternal use of SSRI/SNRI (14082)	Isabelle Robine (FR)	Routine pharmacovigilance	Lundbeck; Eli Lilly; Abbott; GlaxoSmithKline; Organon; Pfizer

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Serotonin–noradrenaline reuptake inhibitors (SNRIs): duloxetine; sibutramine; venlafaxine				