24 September 2015
EMA/PRAC/590240/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 7-10 September 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 7-10 September 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 (21-24 September 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. Bisphosphonates (alendronic acid; alendronic acid, colecalciferol; clodronic acid; etidronic acid; ibandronic; neridronic acid; pamidronic acid; risedronic acid; tiludronic acid; zoledronic acid) - Osteonecrosis of the external auditory canal

Authorisation procedure	Centralised and non-centralised
EPITT No	18256
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	10 September 2015

Recommendation

Bisphosphonates

Changes to product information

Having considered the evidence from clinical trials, the published literature and spontaneous reporting, the PRAC has recommended that the MAHs of alendronic acid, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, zoledronic acid, tiludronic acid and risedronic acid should submit a variation within 2 months to amend the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) as described below (new text underlined):

Summary of Product Characteristics

Section 4.4

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Section 4.8

Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Package Leaflet

Section 4. Possible side effects

Very rare

- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

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

1.2. Leflunomide - Pulmonary hypertension

Authorisation procedure	Centralised
EPITT No	18221
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	10 September 2015

Recommendation

Having considered the available evidence in EudraVigilance, in the literature, the data submitted by the MAH, and the known association of leflunomide with interstitial lung disease, the PRAC has agreed that the MAH(s) of leflunomide-containing medicinal products should submit a variation within 2 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:

Respiratory reactions

Interstitial lung disease, as well as rare cases of pulmonary hypertension ~~has~~ have been reported during treatment with leflunomide (see section 4.8). The risk of ~~its~~ their occurrence ~~is~~ can be increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate.

Section 4.8 – Undesirable effects:

Respiratory, thoracic and mediastinal disorders

[…]

Frequency 'not known': pulmonary hypertension

Package Leaflet

Section 4: Possible side effects

Tell your doctor **immediately** if you experience:

[…]

- ~~a~~ **cough** or **breathing problems** as these may indicate ~~inflammation~~ problems of the lung (interstitial lung disease or pulmonary hypertension);

[…]

Other side effects such as kidney failure, a decrease in the levels of uric acid in your blood, pulmonary hypertension, male infertility […] may also occur with an unknown frequency.

1.3. Thioctic acid - Insulin autoimmune syndrome

Authorisation procedure	Non-centralised
EPITT No	18406
PRAC rapporteur(s)	Marina Dimov Di Giusti (HR)
Date of adoption	10 September 2015

Recommendation

Having considered the available evidence in EudraVigilance and the literature, the PRAC has agreed that the marketing authorisation holders of thioctic acid-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of Products Characteristics

Section 4.4 - Special warnings and precautions for use:

Cases of Insulin Autoimmune Syndrome (IAS) have been reported during treatment with thioctic acid. Patients with human leukocyte antigen genotype such as HLA-DRB1*04:06 and HLA-DRB1*04:03 alleles, are more susceptible to develop IAS when treated with thioctic acid. HLA-DRB1*04:03 allele (susceptibility to IAS odds ratio: 1.6) is especially found in Caucasians, with a higher prevalence in southern than in northern Europe and HLA-DRB1*04:06 allele (susceptibility to IAS odds ratio: 56.6) is especially found in Japanese and Korean patients.

IAS should be considered in the differential diagnosis of spontaneous hypoglycaemia in patients using thioctic acid (see section 4.8).

Section 4.8 - Undesirable effects:

Immune system disorders

Frequency unknown: insulin autoimmune syndrome (see section 4.4)

Package Leaflet

Section 2. What you need to know before you <take> <use> X:

Patients with a certain human leukocyte antigen genotype (which is more frequent in Japanese and Korean patients, but is also found in Caucasians) are more prone to development of insulin autoimmune syndrome (disorder of the blood glucose regulating hormones with pronounced lowering of blood sugar levels) when treated with thioctic acid.

Section 4. Possible side effects:

Frequency unknown: Disorder of the blood glucose regulating hormones with pronounced lowering of blood sugar levels (insulin autoimmune syndrome).

1.4. Trabectedin - Capillary leak syndrome

Authorisation procedure	Centralised
EPITT No	18115
PRAC rapporteur(s)	Torbjörn Callreus (DK)
Date of adoption	10 September 2015

Recommendation

In the light of available evidence from case reports in EudraVigilance and from data submitted by the MAH, the PRAC has agreed that there is a reasonable possibility of a causal relationship between capillary leak syndrome and the use of trabectedin. The PRAC does not believe that additional data from two randomised clinical trials (ET743-OVA-301 and ET743-SAR-3007) submitted by the MAH materially challenges its previous position. Considering the seriousness of the condition, the PRAC maintains that an update of the product information is warranted. Therefore, the MAH for trabectedin 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

Frequency 'uncommon': Cases of suspected capillary leak syndrome have been reported with trabectedin.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Bcr abl tyrosine kinase inhibitors	Hepatitis B virus (HBV) reactivation (18405)	Dolores Montero Corominas (ES)	Supplementary information requested (submission by 11/11/2015)	Novartis Europharm Ltd, Bristol-Myers Squibb Pharma EEIG, Pfizer Limited, ARIAD Pharma Ltd
Clozapine	Myocarditis (18414)	Julie Williams (UK)	Supplementary information requested (submission by 11/11/2015)	Novartis Pharma, Sandoz
Daptomycin	Acute generalised exanthematous pustulosis (AGEP) (18412)	Julie Williams (UK)	Assess in the next PSUR (submission by 20/11/2015)	Novartis Europharm Ltd

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Lenalidomide	Pulmonary alveolar haemorrhage (18300)	Corinne Féchant (FR)	Assess in the next PSUR for thalidomide, lenalidomide and pomalidomide (submission by 18/12/2015)	Celgene Europe Limited
Levetiracetam	Encephalopathy (18423)	Veerle Verlinden (BE)	Assess in the next PSUR (submission by 28/02/2016)	UCB Pharma SA
Methotrexate	Progressive multifocal leukoencephalopathy (PML) (18473)	Doris I. Stenver (DK)	Supplementary information requested (submission by 11/11/2015)	Therakind, Pfizer
Paracetamol; phenylephrine	Pharmacokinetic drug interaction: increased bioavailability of phenylephrine when co-administered with paracetamol (18474)	Veerle Verlinden (BE)	Supplementary information requested (submission by 11/11/2015)	Aspar Pharmaceuticals, Aziende Chimiche Riunite Angelini Francesco, Bayer, Beecham, Boehringer Ingelheim, GlaxoSmithKline, Kern Pharma, Novartis, Phoenix Labs, Reckitt Benckiser
Peginterferon alfa-2a	Guillain-Barré syndrome (18402)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 11/11/2015)	Roche Registration Limited
Pemetrexed	Scleroderma (18383)	Corinne Féchant (FR)	Assess in the frame of the assessment of the Pemetrexed 3-years PSUSA (submission by 31/10/2015)	Eli Lilly Nederland B.V.
Regorafenib	Acute pancreatitis (18440)	Sabine Straus (NL)	Assess in the ongoing PSUR procedure (submission as requested in PSUR preliminary AR of 10 August 2015 by 10/09/2015	Bayer Pharma AG

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
			[EMEA/H/C/PSUSA/00010133/201503])	
Regorafenib	Haemolysis (18437)	Sabine Straus (NL)	Assess in the ongoing PSUR procedure (submission as requested in PSUR preliminary AR of 10 August 2015 by 10/09/2015 [EMEA/H/C/PSUSA/00010133/201503])	Bayer Pharma AG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amikacin	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (18304)	Maia Uusküla (EE)	Monitor in PSUR	Bristol-Myers Squibb
Denosumab	Osteonecrosis of the external auditory canal (18256)	Julie Williams (UK)	Update of risk management plan (RMP)	Amgen Europe B.V.
Digoxin	Mortality in patients with atrial fibrillation (18259)	Carmela Macchiarulo (IT)	No action	Not applicable
Hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in combination; bazedoxifene, oestrogens conjugated	Increased risk of ovarian cancer (18258)	Menno van der Elst (NL)	Comment on product information changes proposed by PRAC	MAHs of medicinal products containing oestrogens (tibolone also considered) and combined oestrogens-progestagens, which are not pharmaceutical forms for vaginal use

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Liraglutide	Medullary thyroid cancer (18292)	Menno van der Elst (NL)	Monitor in PSUR	Novo Nordisk A/S
Sunitinib	Pneumatosis intestinalis (18396)	Carmela Macchiarulo (IT)	Signal to be addressed within the scope of the ongoing PSUR single assessment procedure (PSUSA/00002833/201504)	Pfizer Limited
Tamsulosin	Urinary incontinence (18317)	Sabine Straus (NL)	Monitor in PSUR	Astellas Phama