5 February 2015
EMA/PRAC/734433/2014 Corr.[3]
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 6-9 January 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 6-9 January 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 (19-22 January 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 established procedures and timelines for submission of variation applications pertaining to generic medicinal products are to be followed.

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. Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin – Immune-mediated necrotizing myopathy (IMNM)

Substance (invented name)	Pravastatin (Pravafenix, EMEA/H/C/001243), medicines containing simvastatin, fluvastatin, pitavastatin, atorvastatin or lovastatin
Authorisation procedure	Centralised and Non-centralised
EPITT No	18140
PRAC rapporteur(s)	Arnaud Batz (FR)
Date of adoption	9 January 2015

Recommendation

Having considered the available evidence from the literature, the PRAC has agreed that the MAHs for medicinal products containing atorvastatin, simvastatin, pravastatin, fluvastatin, pitavastatin or lovastatin should submit a variation within 2 months to amend the product informations as described below (new text underlined):

Summary of Product Characteristics (SmPC):

Section 4.4 - Special warnings and precautions for use:

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Section 4.8 – Undesirable effects:

Musculoskeletal disorders:

Frequency not known: Immune-mediated necrotizing myopathy (see section 4.4)

Package Leaflet:

Section 2:

Also tell your doctor or pharmacist if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.

Section 4:

Side effects of unknown frequency: Muscle weakness that is constant.

[2] Translations in EU languages of the adopted PRAC recommendations for update of the product information will be made available to MAHs via the EMA website. The translations will be reviewed by National Competent Authorities of the Member States and thereafter published. It is expected that this will occur within 3 weeks of publishing this document.

1.2. Gadodiamide; Gadopentetic acid; Gadoversetamide – Nephrogenic systemic fibrosis in patients with acute kidney injury

Substance (invented name)	Gadoversetamide (Optimark, EMEA/H/C/000745); Gadodiamide (Omniscan); Gadopentetic acid (Magnevist); and products with the same active substances
Authorisation procedure	Centralised and Non-centralised
EPITT No	408
PRAC rapporteur(s)	Rafe Suvarna (UK)
Date of adoption	9 January 2015

Recommendation

Having considered the available evidence the PRAC has agreed that the MAH of Omniscan, Optimark and Magnevist should submit a variation within 2 months, to amend the product information as described below (new text underlined / text to be removed ~~strikethrough~~). The package leaflets should be updated accordingly. Following the variation of the marketing authorisation for these products, the MAHs for any product with the same active substance should submit a respective variation application.

SmPC changes for Omniscan (gadodiamide) and Magnevist (gadopentetic acid)

4.2 Posology and method of administration

[…]

Renal impairment

<invented name> is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and/or acute kidney injury and in patients in the perioperative liver transplantation period (see section 4.3).

4.3 Contraindications

<invented name> is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m2) and/or acute kidney injury, in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age (see section 4.4).

4.4 Special warnings and precautions for use

[…]

Patients with i~~I~~mpaired renal function

Prior to administration of <invented name>, all patients should be screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of <invented name> and some other gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m2) and/or acute kidney injury. <invented name> is contraindicated in these patients (see section 4.3). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore <invented

name> must not be used ~~in patients with severe renal impairment,~~ in patients in the perioperative liver transplantation period and in neonates (see section 4.3).

SmPC changes for Optimark (gadoversetamide)

4.2 Posology and method of administration

[…]

Renal and hepatic impairment

Optimark is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and/or acute renal injury and in patients who have had liver transplantation or in patients in the perioperative liver transplantation period (see section 4.3).

4.3 Contraindications

[…]

Optimark is contraindicated

- in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and/or acute kidney injury.
- in patients who have had liver transplantation or
- in patients in the perioperative liver transplantation period and
- in neonates up to 4 weeks of age (see section 4.4).

4.4 Special warnings and precautions for use

[…]

Patients with i~~I~~mpaired renal function

Prior to administration of Optimark, all patients should be screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of Optimark and some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR <30ml/min/1.73m²) and/or acute kidney injury. Optimark is contraindicated in these patients (see section 4.3). Patients who have had or are undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore, Optimark must not be used in patients who have had or are undergoing liver transplantation and in neonates (see section 4.3).

1.3. Lithium – Solid renal tumours

Substance (invented name)	Lithium
Authorisation procedure	Non-centralised
EPITT No	18090
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	9 January 2015

Recommendation

In light of the data available, the PRAC has agreed that the evidence is sufficient to conclude that long-term use of lithium may induce microcysts, oncocytomas and collecting duct renal carcinomas. Therefore, the Marketing Authorisation Holders of lithium containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined). In addition, routine pharmacovigilance should be performed in order to better characterise the risk.

SmPC:

4.4 Special warnings and special precautions for use

Renal tumours: Cases of microcysts, oncocytomas and collecting duct renal carcinoma have been reported in patients with severe renal impairment who received lithium for more than 10 years (see Section 4.8).

4.8 Undesirable effects

Renal and urinary disorders:

Frequency unknown: Microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy) (see Section 4.4).

Package leaflet:

2. What you need to know before you <take> <use> <product name>

Warnings and Precautions:

Kidney tumours: Patients with severe kidney impairment who received lithium for more than 10 years may have a risk of developing a benign or malignant kidney tumour (microcysts, oncocytoma or collecting duct renal carcinoma).

4. Possible side effects:

Frequency unknown: Benign/malignant kidney tumours (microcysts, oncocytoma, or collecting duct renal carcinoma) (in long-term therapy).

Homeopathic products containing lithium are not affected by this PRAC recommendation.

1.4. Paroxetine - Aggression

Substance (invented name)	Paroxetine
Authorisation procedure	Non-centralised
EPITT No	18089
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	9 January 2015

Recommendation

Taken into account all available data PRAC agreed that all MAHs for paroxetine containing products should submit a variation within 2 months to amend the product information (section 4.8 of the SmPC and package leaflet) as described below (new text underlined).

SmPC:

Section 4.8 – Undesirable effects:

Psychiatric disorders

Frequency 'not known': aggression

Footnote - cases of aggression were observed in post marketing experience

Package Leaflet:

Section 4 Possible side effects:

Frequency 'not known': aggression

1.5. Valproate and related substances – Mitochondrial toxicity

Substance (invented name)	Valproate and related substances
Authorisation procedure	Non-centralised
EPITT No	18090
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	9 January 2015

Recommendation

In light of the data submitted by the marketing authorisation holders and the advice provided by the Pharmacogenomics Working Party, the PRAC concluded that the evidence is sufficient to support a causal association between valproate and aggravation of underlying mitochondrial diseases, including risk of hepatotoxicity occurring mainly in patients suffering from POLG (polymerase gamma) mutations.

The marketing authorisation holders for valproate (and related substances) containing medicinal products should submit a variation within 2 months to amend the product information as described below (new text underlined).

SmPC:

4.3 Contraindications

Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

4.4 Special warnings and special precautions for use

Patients with known or suspected mitochondrial disease

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Package Leaflet

Section 2. What you need to know before you <take> <use> <product name>

Do not <take> <use> <product name>:

If you have a genetic problem causing a mitochondrial disorder[3] (e.g. Alpers-Huttenlocher syndrome)

Warnings and precautions

Talk to your doctor <or> , <pharmacist> <or nurse> before <taking> <using> <product name>:

You know that there is a genetic problem causing a mitochondrial disorder[3] in your family.

[3] The initial version published on 27/01/2015 read: 'caused by a mitochondrial disorder' (amended on 05/02/2015).

2. Recommendations for submission of supplementary information

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a **causal relationship** between the medicine and the reported adverse event.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Denosumab	Deafness (18175)	Ulla Wändell-Liminga (SE)	Supplementary information requested (submission by 07/03/2015)	Amgen Europe B.V.
Leflunomide	Colitis (18189)	Sabine Straus (NL)	Supplementary information requested (submission by 07/03/2015)	Sanofi-aventis Deutschland GmbH
Olanzapine	Angle closure glaucoma (18159)	Terhi Lehtinen (FI)	Supplementary information requested (submission by 07/03/2015)	Eli Lilly Nederland B.V.
Sildenafil	Pulmonary haemorrhage in off label paediatric use (18183)	Menno van der Elst (NL)	Supplementary information requested (submission by 07/03/2015)	Pfizer Limited
Sofosbuvir and/or daclatasvir	Arrhythmia (18177)	Margarida Guimarães (PT)	Supplementary information requested (submission by 07/03/2015)	Bristol-Myers Squibb Pharma EEIG, Gilead Sciences International Ltd

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Benzodiazepines	Alzheimer's disease (18195)	Doris Stenver (DK)	Routine pharmacovigilance	MAHs of benzodiazepines containing products
Clopidogrel	Safety of dual antiplatelet therapy (18184)	Margarida Guimarães (PT)	No action at this stage	Sanofi Clir SNC
Latanoprost	Increased reporting of eye disorders, in particular eye irritation, after change of formulation (18068)	Julie Williams (UK)	No action at this stage	Pfizer
Recombinant Factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa	Inhibitor development in previously untreated patients (18134)	Brigitte Keller-Stanislawski (DE)	No action at this stage	Bayer Pharma AG, Baxter AG, Pfizer Limited, various
Teriparatide	Non-uraemic calciphylaxis (18056)	Julie Williams (UK)	RMP update (addition of a potential risk)	Eli Lilly Nederland B.V.