Thursday 22 January 2015
EMA/PRAC/62352/2015
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals for update of the product information

Adopted at the 6-9 January 2015 PRAC

1. Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin – Immune-mediated necrotizing myopathy (IMNM) (EPITT no 18140)

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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5525
Send a question via our website www.ema.europa.eu/contact

2. Gadodiamide; gadopentetic acid; gadoversetamide – Nephrogenic systemic fibrosis in patients with acute kidney injury (EPITT no 408)

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).

3. Lithium – Solid renal tumours (EPITT no 18090)

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.

4. Paroxetine – Aggression (EPITT no 18089)

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

5. Valproate and related substances – Mitochondrial toxicity (EPITT no 17956)

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 (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 in your family.