15 December 2016
EMA/PRAC/740369/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

# PRAC recommendations on signals

## Adopted at the PRAC meeting of 28 November-1 December 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 28 November-1 December 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 (12-15 December 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.

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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. Acenocoumarol; phenprocoumon; fluindione; phenindione – Calciphylaxis*

| | |
|---|---|
| **Authorisation procedure** | Non centralised |
| **EPITT No** | 18710 |
| **PRAC rapporteur(s)** | Martin Huber (DE) |
| **Date of adoption** | 1 December 2016 |

## Recommendation

Having considered the available evidence from EudraVigilance, the literature, the analysis submitted by Meda Pharma, Merck Santé S.A.S, Merus Labs Luxco and Mercury Pharma Group, 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 vitamin K antagonists. The PRAC has agreed that the MAH(s) of acenocoumarol, phenprocoumon, fluindione and phenindione 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 (acenocoumarol, phenprocoumon)**

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 vitamin K antagonists including <product name>, 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 <product name>.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'not known': Calciphylaxis

**Package leaflet (acenocoumarol, phenprocoumon)**

4 – Possible side effects

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

[…]

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

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

**Summary of product characteristics (fluindione, phenindione)**

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 vitamin K antagonists, 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 <product name>.

## *1.2. Methylphenidate – Priapism*

| | |
|---|---|
| **Authorisation procedure** | Non centralised |
| **EPITT No** | 18719 |
| **PRAC rapporteur(s)** | Julie Williams (UK) |
| **Date of adoption** | 1 December 2016 |

## Recommendation

Having considered the cases from the safety databases of the MAHs of methylphenidate containing products, including from the literature, the PRAC has concluded that there is sufficient evidence to amend the product information with priapism associated disorders, and that the MAH(s) of medicinal products containing methylphenidate (including all formulations) 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

Priapism. Prolonged and painful erections have been reported in association with methylphenidate products, mainly in association with a change in the methylphenidate treatment regimen. Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

4.8. Undesirable effects

Reproductive system and breast disorders

Priapism, erection increased and prolonged erection

Frequency: not known

**Package leaflet**

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

Warnings and precautions

During treatment, boys and adolescents may unexpectedly experience prolonged erections. This may be painful and can occur at any time. It is important to contact your doctor straight away if your erection lasts for longer than 2 hours, particularly if this is painful.

4 – Possible side effects

Prolonged erections, sometimes painful, or an increased number of erections

Frequency: not known

## *1.3. Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole ; pantoprazole; rabeprazole – Gastric polyps*

| | |
|---|---|
| **Authorisation procedure** | Centralised and non centralised |
| **EPITT No** | 18725 |
| **PRAC rapporteur(s)** | Qun-Ying Yue (SE) |
| **Date of adoption** | 1 December 2016 |

## Recommendation

Having considered the data from EudraVigilance and literature case reports (including cases with positive de-challenge), as well as the results of two systematic reviews with meta-analysis published in 2016 (Tran-Duy A et al. and Martin FC et al.), considering also the pathophysiologic mechanism of the class of the proton pump inhibitors when used for long treatment periods, the PRAC has recommended that the MAHs of the proton pump inhibitors (i.e. esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) should submit a variation within 3 months, to add 'fundic gland polyps' to the product information as described below (new text underlined):

**Summary of product characteristics (both prescription and non-prescription)**

4.8. Undesirable effects

Gastrointestinal disorders: Fundic gland polyps (benign)

Frequency: common

**Package leaflet (both prescription and non-prescription)**

4 – Possible side effects

Benign polyps in the stomach

Frequency: common

### *1.4. Vildagliptin; Vildagliptin, metformin– Pemphigoid*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 18692 |
| **PRAC rapporteur(s)** | Qun-Ying Yue (SE) |
| **Date of adoption** | 1 December 2016 |

## Recommendation

Having considered the available evidence from case reports in EudraVigilance and in the literature, including the disproportionality score for vildagliptin being the highest of the iDPP-4 class, the PRAC has agreed that the MAH of vildagliptin-containing products (Novartis Europharm Limited), should submit a variation within 2 months, to amend the product information as described below (new text underlined):

**Summary of product characteristics**

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

~~Bullous or exfoliative~~ Exfoliative and bullous skin lesions, including bullous pemphigoid

Frequency: not known

# 2. Recommendations for submission of supplementary information

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Albiglutide | Acute kidney injury (18778) | Julie Williams (UK) | Supplementary information requested (submission by 1 February 2017) | GlaxoSmithKline Trading Services |
| Brentuximab vedotin | Cytomegalovirus (CMV) reactivation (18789) | Sabine Straus (NL) | Supplementary information requested (submission by 1 February 2017) | Takeda Pharma A/S |
| Dabrafenib; trametinib | Sepsis (18779) | Ulla Wändel Liminga (SE) | Supplementary information requested (submission by 1 February 2017) | Novartis Europharm Ltd |

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Daratumumab | Tumour lysis syndrome (TLS) (18777) | Leonor Chambel (PT) | Assess in the first PSUR (PSUSA/00010498/201611 - submission by 24 January 2017) | Janssen-Cilag International NV |
| Leflunomide; teriflunomide | Falsely decreased ionised calcium levels (18787) | Sabine Straus (NL) | Supplementary information requested (submission by 1 February 2017) | Sanofi-Aventis; Medac |
| Pirfenidone | Colitis (18793) | Julie Willams (UK) | Supplementary information requested (submission by 1 February 2017) | Roche Registration Limited |
| Temozolomide | Meningoencephalitis herpetic (18785) | Martin Huber (DE) | Supplementary information requested (submission by 1 February 2017) | Merck Sharp & Dohme Limited |

## 3. Other recommendations

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Meropenem; ciprofloxacin | Incompatibility leading to possible precipitation when co-administered intravenously (18790) | Jan Neuhauser (AT) | No action at this stage | Not applicable |