24 July 2014
EMA/PRAC/425079/2014
Pharmacovigilance Risk Assessment Committee

# PRAC recommendations on signals

## Adopted at the PRAC meeting of 7-10 July 2014

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 July 2014 (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 July 2014) 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

## *1.1. Bupropion – Pancytopenia*

| | |
|---|---|
| **Substance (invented name)** | Bupropion |
| **Authorisation procedure** | Non-centralised |
| **EPITT No** | 17727 |
| **PRAC rapporteur** | Sabine Straus (NL) |
| **Date of adoption** | 10 July 2014 |

### Recommendation

Having assessed the data provided by the MAH, the PRAC considered the cases reported with positive de-challenge and re-challenge to be relevant as a clear indicator of causality. The PRAC recommended that the MAH(s) of bupropion containing products should submit a variation within 2 months to the NCAs, to amend the Product Information (PI) as described below (new text underlined):

**Summary of Product Characteristics:**

Section 4.8 – Undesirable effects:

Blood and lymphatic system disorders: anaemia, leukopenia and thrombocytopenia
Frequency: Unknown

**Package Leaflet:**

Section 4 – Possible side effects

Other side effects

Other side effects have occurred in a small number of people but their exact frequency is unknown:

- reduced numbers of red blood cells (anaemia), reduced numbers of white blood cells (leucopenia) and reduced numbers of platelets (thrombocytopenia).

NB: This proposal is based on current approved EU text for the package leaflet of Wellbutrin XR/Zyban.

## 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 |
|---|---|---|---|---|
| Rivaroxaban | Spontaneous splenic rupture/haemorrhage (18020) | Qun-Ying Yue (SE) | Assess in the next PSUR (submission by 24/11/2014) | Bayer Pharma AG |
| Sildenafil | Increased risk of incident melanoma (17997) | Menno van der Elst (NL) | Supplementary information requested (submission by 06/09/2014) | Pfizer Limited |

## 3. Other recommendations

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Azithromycin | Potentially fatal heart events (16156) | Terhi Lehtinen (FI) | Post-Authorisation Safety Study to be submitted (by 31/08/2014) | Pfizer Limited |
| Bisphosphonates, strontium ranelate | Heart valves disorders (13832) | Julie Williams (UK) | No action at this stage | Not applicable |
| Buprenorphine, transdermal patches | Skin depigmentation (18040) | Isabelle Robine (FR) | Monitor in PSUR | MAHs of buprenorphine transdermal patches |
| Calcium channel blockers | Breast cancer risk (17750) | Ulla Wändel Liminga (SE) | The available evidence does not support a causal association; no action for MAH. | Not applicable |
| Tacrolimus, Febuxostat | Potential drug-drug interaction between systemic tacrolimus and febuxostat (17809) | Almath Spooner (IE) | Monitor in PSUR | Astellas, Menarini |