26 October 2020[1]
EMA/PRAC/513083/2020
Pharmacovigilance Risk Assessment Committee (PRAC)

# PRAC recommendations on signals

## Adopted at the 28 September-1 October 2020 PRAC meeting

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 September-1 October 2020 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] 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 October 2020) 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.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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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.

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[3]

## *1.1. Citalopram; desvenlafaxine; escitalopram; fluoxetine; fluvoxamine; milnacipran; paroxetine; sertraline; venlafaxine; vortioxetine – Postpartum haemorrhage*

| | |
|---|---|
| **Authorisation procedure** | Centralised and non-centralised |
| **EPITT No** | 19552 |
| **PRAC rapporteur(s)** | Ulla Wändel Liminga (SE) |
| **Date of adoption** | 1 October 2020 |

### Recommendation *[see also section 3]*

The PRAC considered the known association between bleeding events with selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitor (SNRIs), as well as with vortioxetine and further evidence from several observational studies (namely in reviews by Bruning et al 2015 and Jiang et al 2016, as well as from Heller at al 2017, Huybrechts at al 2020, Palmsten et al in 2013 and 2020 and Skalkidou et al in 2020) about occurrence of postpartum haemorrhage in association with antidepressants' use by pregnant women, particularly SSRIs and SNRIs.

Based on evidence reviewed, no updates of the product information of mirtazapine, trazodone, amitriptyline and bupropion (including its combination with naltrexone) are warranted at present. The innovator MAH of amitriptyline (Lundbeck) is requested to monitor haemorrhage and post-partum haemorrhage events in in next PSUSA procedure. The wording already agreed for duloxetine remains adequate.

The PRAC considered the comments on the proposed wording received from the innovator MAHs concerned by this procedure as well as their discussion on frequency of the occurrence of the postpartum haemorrhage event and agreed that the MAH(s) of citalopram-, desvenlafaxine-, escitalopram-, fluoxetine-, fluvoxamine-, milnacipran-, paroxetine-, sertraline-, venlafaxine-containing products should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text <u>underlined</u>).

**Summary of product characteristics**

4.4. Special warnings and precautions for use

<u>SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).</u>

4.6. Fertility, pregnancy and lactation

<u>Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).</u>

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

4.8. Undesirable effects

*SOC Reproductive system and breast disorders*: postpartum haemorrhage*; frequency not known

Add a footnote under the Table that this event is a class effect: * This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).

**Package leaflet**

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

Warnings and precautions

Talk to your doctor before taking <product name>, especially if you have:

- History of bleeding disorders […], or if you are pregnant (see 'Pregnancy'[4])

Pregnancy[4]

If you take <product name> near the end of your pregnancy there may be an increased risk of heavy vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders. Your doctor or midwife should be aware that you are taking <product name> so they can advise you.

4. Possible side effects

[…]

Frequency not known

• Heavy vaginal bleeding shortly after birth (postpartum haemorrhage), see Pregnancy[4] in section 2 for more information

Having considered the existing wording in the product information of Brintellix as well as the comments received from the innovator MAH concerned by this procedure, the PRAC agreed that the MAH should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined).

**Summary of product characteristics**

4.4. Special warnings and precautions for use

Haemorrhage

Bleeding abnormalities, such as ecchymoses, purpura and other haemorrhagic events, such as gastrointestinal or gynaecological bleeding, have been reported rarely with the use of antidepressants with serotonergic effect, including vortioxetine. SSRIs/SNRIs may increase the risk of postpartum haemorrhage, and this risk could potentially apply also to vortioxetine (see section 4.6). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function [e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA)] (see section 4.5) and in patients with known bleeding tendencies/disorders.

[4] In some medicinal products the relevant section may be called 'Pregnancy, breast-feeding and fertility'.

4.6. Fertility, pregnancy and lactation

Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to an SSRI or SNRI within the month prior to birth. Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action (see section 4.4).

**Package leaflet**

2. What you need to know before you take Brintellix

Warnings and precautions

Talk to your doctor or pharmacist before taking Brintellix if you:

- have a tendency to bleed or bruise easily, or if you are pregnant (see 'Pregnancy, breast-feeding and fertility')

**Pregnancy, breast-feeding and fertility**

If you take Brintellix near the end of your pregnancy there may be an increased risk of heavy vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders. Your doctor or midwife should be aware that you are taking Brintellix so they can advise you.

## *1.2. Pembrolizumab – Sjogren's syndrome*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19564 |
| **PRAC rapporteur(s)** | Menno van der Elst (NL) |
| **Date of adoption** | 1 October 2020 |

## Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the association of pembrolizumab with Sjogren's syndrome, the PRAC has agreed that the Marketing Authorisation Holder (MAH) of Keytruda (Merck Sharp & Dohme B.V.), 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

Tabulated list of adverse reactions

Table 2: Adverse reactions in patients treated with pembrolizumab

| | Monotherapy | Combination with chemotherapy | Combination with axitinib |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Very common | musculoskeletal pain[x], arthralgia | musculoskeletal pain[x], arthralgia | musculoskeletal pain[x], arthralgia, pain in extremity |
| Common | pain in extremity, myositis[y], arthritis[z] | myositis[y], pain in extremity, arthritis[z] | myositis[y], arthritis[z], tenosynovitis[aa] |
| Uncommon | tenosynovitis[aa] | tenosynovitis[aa] | Sjogren's syndrome |
| Rare | Sjogren's syndrome | Sjogren's syndrome | |

**Package leaflet**

4. Possible side effects

The following side effects have been reported with pembrolizumab alone:

**Rare (may affect up to 1 in 1,000 people)**

- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

The following side effects have been reported in clinical studies with pembrolizumab in combination with chemotherapy:

**Rare (may affect up to 1 in 1,000 people)**

- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

The following side effects have been reported in clinical studies with pembrolizumab in combination with axitinib:

**Uncommon (may affect up to 1 in 100 people)**

- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

## 2. Recommendations for submission of supplementary information

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Efavirenz | Microcephaly (19595) | Ana Sofia Martins (PT) | Supplementary information requested (submission by 9 December 2020) | Bristol-Myers Squibb Pharma EEIG; Merck Sharp & Dohme B.V. |
| Isatuximab | Anaphylactic reaction (19598) | Eva A. Segovia (ES) | Assess in the next PSUR (submission by 10 November 2020) | Sanofi-Aventis Groupe |
| Prednisolone and prednisone | Bradycardia (19613) | Anette Kirstine Stark (DK) | Supplementary information requested (submission by 9 December 2020) | Takeda; Mundipharma |
| Remdesivir | Acute kidney injury | Eva Jirsová (CZ) | Supplementary information requested (submission by 9 December 2020) | Gilead Sciences Ireland UC |

## 3. Other recommendations

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Amitriptyline; bupropion (incl. its combination with naltrexone); citalopram; desvenlafaxine; duloxetine; escitalopram; fluoxetine; fluvoxamine; milnacipran; mirtazapine; paroxetine; sertraline; trazodone; venlafaxine; vortioxetine | Postpartum haemorrhage (19552) | Ulla Wändel Liminga (SE) | · See section 1.1 | MAHs of products containing citalopram, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine, vortioxetine |
| | | | · No update of the product information warranted | · MAHs of products containing mirtazapine, trazodone, amitriptyline and bupropion (incl. its combination with naltrexone) |
| | | | · Monitor haemorrhage and postpartum haemorrhage events in the next PSUSA procedure | · Lundbeck (innovator MAH of amitriptyline) |
| | | | · No action (wording already agreed remains adequate) | · MAHs of duloxetine containing products |