24 October 2022[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 26-29 September 2022 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 26-29 September 2022 (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 (10-13 October 2022) 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] 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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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. Codeine, ibuprofen – Renal tubular acidosis and hypokalaemia

Authorisation procedure	Non-centralised
EPITT No	19820
PRAC Rapporteur	Rhea Fitzgerald (IE)
Date of adoption	29 September 2022

Recommendation

Having considered the available evidence , including the responses provided by the innovator Marketing Authorisation Holders (MAHs) of codeine/ibuprofen (Viatris and Reckitt Benckiser) to the PRAC list of questions, the PRAC has agreed that all MAHs of the fixed combination codeine/ibuprofen-containing medicinal products should submit a variation within 2 months of the publication date of the PRAC recommendation, to amend the product information as described below (new text underlined/text to be removed with ~~strikethrough~~).

Summary of product characteristics

4.4 - Special warnings and precautions for use

Renal: Renal impairment as renal function may deteriorate (see sections 4.3 and 4.8). There is a risk of renal impairment in dehydrated children and adolescents.

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component (see warning on Opioid use disorder, section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Opioid use disorder (abuse and dependence)

~~Codeine is a narcotic analgesic. No more than the stated dose of this medicine should be taken~~. Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine. Abuse or intentional misuse of <Product name> may result in overdose and/or death. ~~Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction), and result in Withdrawal symptoms, such as restlessness and irritability may occur once the drug is stopped. It is important to consult a doctor if a patient experiences the need to use this product all the time.~~

Serious clinical outcomes, including fatalities, have been reported in association with abuse and dependence with codeine/ibuprofen combinations, particularly when taken for prolonged periods at higher than recommended doses. These have included reports of gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia, renal failure, renal tubular acidosis and severe hypokalaemia associated with the ibuprofen component.

Patients should be informed about the risks and signs of OUD as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.

Withdrawal symptoms, such as restlessness and irritability may occur once the drug is stopped.

[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

System Organ Class	Frequency	Adverse Events
Metabolism and Nutrition Disorders	Not known Not known	Decreased Appetite Hypokalaemia* (*The reference numbers for the description of the selected Adverse reaction should be updated throughout the table)*
Renal and urinary disorders	Very rare Not known Not known	Acute renal failure Ureteric colic, dysuria Renal tubular acidosis*

Description of Selected Adverse Reactions

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses due to dependence on the codeine component.

4.9 - Overdose

Symptoms

[…]

In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Exacerbation of asthma is possible in asthmatics.

Package leaflet

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE <Product Name> TABLETS/CAPSULES

Warnings and Precautions

The below wording should be presented prominently as a boxed warning.

<Product name> contains codeine, which is an opioid medicine.

Repeated use of <Product name> may result in you becoming accustomed to it (needing to take higher doses). Repeated use of <Product name> may also lead to dependence, abuse and addiction, which may result in life-threatening overdose.
If you are taking <Product name> for longer than the recommended time or at higher than recommended doses you are at risk of serious harms. These include serious harms to the stomach/gut and kidneys, as well as very low levels of potassium in your blood. These can be fatal (see section 4).

If you experience any of the following signs whilst taking <Product name>, talk to your doctor or pharmacist as it could be an indication that you are dependent or addicted.
- You need to take this medicine for longer than advised
- You need to take more than the recommended dose
- You are using this medicine for reasons other than medical reasons, for instance, 'to stay calm' or to 'help you sleep'
- You have made repeated, unsuccessful attempts to quit or control the use of this medicine
- When you stop taking this medicine you feel unwell, and you feel better once taking this medicine again ('withdrawal effects')

4 - POSSIBLE SIDE EFFECTS

Like all medicines, <Product Name> can cause side-effects, although not everybody gets them. Tell your doctor or pharmacist if you notice any of the following:

[…]
- Liver, kidney problems or difficulty urinating

[…]
- Skin becomes sensitive to light

<Product Name>, especially when taken at higher than recommended doses or for a prolonged period of time, can cause damage to your kidneys and affect them removing acids properly from your blood into the urine (renal tubular acidosis). It can also cause very low levels of potassium in your blood (see section 2). This is a very serious condition and will require immediate treatment. Signs and symptoms include muscle weakness and light-headedness.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Bosutinib	Interstitial lung disease (ILD) (19843)	Martin Huber (DE)	Supplementary information requested (submission by 7 December 2022)	Pfizer Europe MA EEIG
Colistimethate sodium[4]	Pseudo-Bartter syndrome (19845)	Adam Przybyłkowski (PL)	Supplementary information requested (submission by 7 December 2022)	Sanofi-Aventis, Teva, UCB Pharma
Enfortumab vedotin	Interstitial lung disease (ILD) (19842)	Eva Jirsová (CZ)	Assess in the next PSUR (submission by 26 February 2023)	Astellas Pharma Europe B.V.
Nivolumab	Morphoea (19839)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 December 2022)	Bristol-Myers Squibb Pharma EEIG
Selpercatinib	Hypothyroidism (19847)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 17 January 2023)	Eli Lilly Nederland B.V.

[4] For intravenous use only

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Gemtuzumab ozogamicin	Atypical haemolytic reactions (19788)	Márcia Silva (PT)	Monitor in PSUR	Pfizer Europe MA EEIG
Rivaroxaban	Pemphigoid (19785)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	MAHs of rivaroxaban containing products
Selective serotonin reuptake transporter inhibitors (SSRIs): citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline; and Serotonin-norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine; duloxetine; milnacipran; venlafaxine; and Mirtazapine; vortioxetine	Pulmonary hypertension (19772)	Liana Gross-Martirosyan (NL)	Routine pharmacovigilance	MAHs of SSRI, SNRI, mirtazapine or vortioxetine containing products
Temozolomide	Progressive multifocal leukoencephalopathy (PML) (19814)	Martin Huber (DE)	Routine pharmacovigilance	MAHs of temozolomide containing products