24 October 2022[1]
EMA/PRAC/838103/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 26-29 September 2022 PRAC

No product with an Icelandic marketing authorisation falls within the scope of this PRAC recommendation. Therefore the text has not been translated into Icelandic. / Ekkert lyf með íslenskt markaðsleyfi fellur undir þessa ákvörðun PRAC. Textarnir hafa því ekki verið þýddir á íslensku.

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found ***here*** (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

1. Codeine, ibuprofen – Renal tubular acidosis and hypokalaemia (EPITT no 19820)

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

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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

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.

4.8 - Undesirable effects

System Organ Class	Frequency	Adverse Events
Metabolism and Nutrition Disorders	[…] Not known	[…] Hypokalaemia* (*The reference numbers for the description of the selected Adverse reaction should be updated throughout the table)*
Renal and urinary disorders	[…] Not known	[…] 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:

[…]
- 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.