# SAFETY ALERT

**DRAP SAFTEY ALERT NO. 43**

## Safety Alert of Risk of Serious Renal and Gastrointestinal Harms with Codeine plus Ibuprofen Drug Combination.

**Date: 20th of October, 2023.**

## Target Audience:

- Manufacturers and importers of drug combinations containing codeine with ibuprofen;
- Healthcare professionals; and
- Patients, consumers or caregivers.

## Background:

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in September 2022 recommended a change to the product information for codeine with ibuprofen combination medicines to include a warning of serious harms, including death, particularly when taken for prolonged periods at higher than recommended doses.

The PRAC reviewed several cases of renal, gastrointestinal and metabolic toxicities that have been reported in association with cases of abuse of and dependence on codeine with ibuprofen combinations, some of which have been fatal. The PRAC found that, when taken at higher than recommended doses or for a prolonged period of time, codeine with ibuprofen can cause damage to the kidneys, preventing them from removing acids properly from the blood into the urine (renal tubular acidosis). Kidney malfunction can also cause hypokalaemia, which in turn may cause symptoms such as muscle weakness and light-headedness. Therefore, renal tubular acidosis and hypokalaemia will be added to the product information as new adverse effects. The PRAC noted that medicines containing a combination of codeine and ibuprofen are authorised at the national level and in some countries these medicines are available without medical prescription. The PRAC considered that prescription-only medicine status would be the most effective risk minimisation measure to mitigate the harm associated with abuse and dependence of these products.

## Action in Pakistan:

The case was discussed in the 3rd meeting of PRAEC, held on the 8th of September, 2023, which

decided as per Rule 10(1)(h)(iv) of Pharmacovigilance Rules, 2022 that registration holders of Codeine with Ibuprofen combination should include information about serious harms (renal, gastrointestinal and metabolic toxicities) including death, particularly when taken for prolonged periods at higher than recommended doses in the warning and precaution section, and to add renal tubular acidosis and hypokalaemia as adverse drug reactions in the prescribing information/ label of codeine with ibuprofen combination.

## Therapeutic Goods Affected.

**Name: Codeine with ibuprofen** is a combination of opioid (codeine) and anti-inflammatory (ibuprofen), which is used to treat pain. Repeated use of codeine with ibuprofen may lead to dependence and abuse due to the codeine component.

## Advice for patients.

Medicine containing codeine with ibuprofen should be used for the duration as recommended by doctors as it may lead to dependence, abuse and addiction, which may result in a life-threatening overdose. If you are taking for longer than the recommended time or at higher than recommended doses you are at risk of serious harm. These include serious harm to the stomach/gut and kidneys, as well as very low levels of potassium in your blood. These can be fatal.

If you experience any of the following signs whilst taking these medicines 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 you take this medicine again ('withdrawal effects')

## Advice for healthcare professionals.

Healthcare professionals are informed that 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. Presenting signs and symptoms included a reduced level of consciousness and generalised weakness. Ibuprofen-induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

## Guidelines for reporting Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with drug combination of codeine with ibuprofen to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) through the Med Vigilance E-Reporting System available on the DRAP website. Similarly, ADRs can also be reported through Med Safety App which is available for download from the App Store (for iOS devices) and Google Play (for Android devices).

## References:


- Minutes of 3rd meeting of Pharmacovigilance Risk Assessment Expert Committee.
- EMA-Europe: Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 26-29 September 2022.
- EMA-Europe: New product information wording – Extracts from PRAC recommendations on signals