HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Nurofen Plus (codeine/ibuprofen) – Serious clinical harms, including renal tubular acidosis and severe hypokalaemia, following prolonged use of codeine/ibuprofen at higher than recommended doses

Nurofen Plus (codeine/ibuprofen) is indicated in patients older than 12 years of age for short-term treatment of acute, moderate pain which is not relieved by other analgesics alone, such as rheumatic and muscular pain, backache, migraine, dental pain, dysmenorrhea, feverishness, and symptoms of cold and flu.

Nurofen Plus should be used at the lowest effective dose for the shortest period of time. The maximum daily dose should not exceed 6 tablets in 24 hours. The duration of treatment should be limited to 3 days and if no effective pain relief is achieved, patients should be advised to consult a doctor.

A recent review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), has identified case reports of severe hypokalaemia and renal tubular acidosis (RTA) with codeine/ibuprofen combinations following prolonged use at higher than recommended doses in the context of dependence/addiction. Confirming the diagnosis of RTA is often delayed resulting in suboptimal treatment.[1] Presenting signs and symptoms in patients diagnosed with RTA/hypokalaemia include reduced level of consciousness and generalised weakness. The frequency of RTA/hypokalaemia associated with Nurofen Plus is unknown from the available safety data.

Other types of serious clinical harms, including fatalities, have been reported in the post-marketing setting in association with abuse and dependence with codeine/ibuprofen combinations. These have included reports of gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia and renal failure. Gastrointestinal and renal toxicities are well established NSAID class effects and are known adverse drug reactions of codeine/ibuprofen combination products, typically associated with patients who have clinical risk factors for these effects. However, recent case reports have highlighted that these adverse reactions may also occur in patients taking codeine/ibuprofen as a result of exposure to ibuprofen at higher than recommended doses and following prolonged use due to dependence on the codeine component.

Following a review of the available safety data, PRAC has recommended updating the product information* for Nurofen Plus to reflect the new risks of RTA and hypokalaemia, including updated warnings and adverse reactions. In addition, warnings in product information will be strengthened regarding the risks of tolerance, abuse, and physical and psychological dependence upon repeated administration of opioids such as codeine. Accompanying warnings will be introduced regarding other serious clinical harms including fatal harms following prolonged use of codeine/ ibuprofen at higher than recommended doses due to dependence on codeine and to advise patients regarding the risks and signs of addiction/dependence with Nurofen Plus.

Advice to Healthcare Professionals

- Patients should be informed of the risks of addiction/dependence with Nurofen Plus and the potential for serious clinical consequences, including gastrointestinal, renal and metabolic harms.
- Patients should be advised to contact their doctor or pharmacist if they experience any of the following signs of addiction/dependence with Nurofen Plus:
  - Needs to take it for longer than advised (more than 3 days).
  - Needs to take more than the recommended dose (more than 6 tablets daily).
  - Takes it for 'non-medical' reasons (e.g. to aid sleep or to reduce feelings of anxiety).
  - Has made repeated, unsuccessful attempts to quit or control use.
  - Feels unwell once stops taking it and feels better once taking it again (withdrawal effects).

Reporting suspected adverse reactions is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions, including cases of addiction/dependence via HPRA Pharmacovigilance, website: www.hpra.ie. All adverse reaction reports, including suspected addiction/dependence, even in the absence of other adverse reactions, provide important information.

Key Message

- Nurofen Plus (codeine/ibuprofen) should be used at the lowest effective dose for the shortest period of time. The maximum daily dose should not exceed 6 tablets in 24 hours. The duration of treatment should be limited to 3 days.
- Cases of severe hypokalaemia and renal tubular acidosis (RTA) have been reported typically following prolonged use of codeine/ibuprofen at higher than recommended doses in patients who have become dependent on the codeine component.
- Presenting signs and symptoms in patients diagnosed with RTA/hypokalaemia include reduced level of consciousness and generalised weakness.
- Other serious clinical harms including gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia and renal failure have been reported in association with cases of abuse and dependence for codeine/ibuprofen combinations, some of which have been fatal.
- Patients should be informed of the risks and signs of addiction/dependence with Nurofen Plus (codeine/ibuprofen) and the potential serious clinical harms as a result.
- Patients should be advised to speak to their doctor or pharmacist if they experience signs of addiction/dependence with Nurofen Plus.

** The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie*

References: 1. Yaxley et al. Review of diagnostic evaluation of Renal Tubular Acidosis. Ochsner J, 2016 Winter. 16(4): 525–530