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28 Mar 2023

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 due to codeine dependence

Dear Healthcare Professional,

Reckitt Benckiser Ltd in agreement with the European Medicines Agency and the Malta Medicines Authority would like to inform you of the following:

Summary

- **Cases of severe hypokalaemia and renal tubular acidosis 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.**

- **Renal tubular acidosis should be considered in patients taking Nurofen Plus with unexplained hypokalaemia and metabolic acidosis, symptoms of which include reduced levels 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 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 (see below).**

Signs of addiction/dependence in patients taking Nurofen Plus

- Needs to take Nurofen Plus 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 the use of Nurofen Plus
- Feels unwell once stops taking Nurofen Plus, and feels better once taking it again (withdrawal effects)

Background on the safety concern

Nurofen Plus is indicated for the relief of pain in such conditions as: rheumatic and muscular pain, backache, migraine, dental pain, dysmenorrhoea, feverishness, symptoms of cold and flu. This product is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone.

Cases of severe hypokalaemia and renal tubular acidosis (RTA) have been reported in the post-marketing setting with codeine/ibuprofen combinations following prolonged use at higher than

recommended doses in the context of dependence/addiction. RTA occurs as a consequence of impaired urinary acidification and is characterised by normal anion gap metabolic acidosis[1,2,3]. 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. Ibuprofen induced RTA should be considered in patients taking Nurofen Plus with unexplained hypokalaemia and metabolic acidosis.

A review of the available data was conducted by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) and included cases in the published literature as well as post-marketing reports. The frequency of RTA/hypokalaemia 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.

Patients should be informed of the risks and signs of addiction/dependence with Nurofen Plus and of these serious clinical consequences. Patients should be advised to contact their doctor or pharmacist if they need to take Nurofen Plus for more than the recommended dose or for longer than the recommended duration, or if they have any signs of addiction/dependence. 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.

The product information (SmPC and package leaflet) for Nurofen Plus will be updated to reflect the new risks of renal tubular acidosis 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.

Call for reporting

Healthcare professionals and patients should report any adverse reactions, suspected adverse drug reactions (side effects) or medication errors associated with the use of Nurofen Plus (codeine/ibuprofen) using the Malta Medicines Authority ADR reporting form available online at http://www.medicinesauthority.gov.mt/adrportal and sent to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or sent by email to postlicensing.medicinesauthority@gov.mt.

Adverse events should also be reported to Charles de Giorgio vigilance department via pv@charlesdegiorgio.com, or +356 9974 1387.

Company contact point

- Charles de Giorgio vigilance department e-mail address: pv@charlesdegiorgio.com
- Charles de Giorgio vigilance department phone number: +356 9974 1387.

Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer
This Direct Healthcare Professional Communication has been submitted to you on behalf of Reckitt Benckiser Ltd.

The MMA receives the relevant contact details from both the Medical Council and the Pharmacy Council. Should you wish to amend your details including address, you are asked to contact the Medical Council or Pharmacy Council directly, as may apply.

References

1. Yaxley et al. Review of diagnostic evaluation of Renal Tubular Acidosis. Ochsner J, 2016 Winter. 16(4): 525–530.
2. Giglio, S., Montini, G., Trepiccione, F. et al. Distal renal tubular acidosis: a systematic approach from diagnosis to treatment. J Nephrol. 2021. 34: 2073–2083.
3. Palmer BF et al. Renal Tubular Acidosis and Management strategies: A Narrative Review. Adv Ther. 2021. 38 (2): 949 – 968.