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HPRA DRUG SAFETY NEWSLETTER

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In this edition

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.

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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.*

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Leuprorelin-containing depot medicines – risk of idiopathic intracranial hypertension (pseudotumor cerebri)

Leuprorelin* is a gonadotropin releasing hormone agonist used in the treatment of prostate cancer, breast cancer and conditions that affect the female reproductive system (e.g. endometriosis, symptomatic uterus myomatosus, uterine fibrosis and early puberty). As part of a recent review by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) of the available safety data for depot formulations of leuprorelin, a potential risk of idiopathic intracranial hypertension (IIH) was identified.

Also known as pseudotumor cerebri, IIH, is a disorder defined by clinical features of elevated intracranial pressure without radiological evidence of an intracranial mass, infection, vascular abnormality, hydrocephalus or changes in the level of consciousness. The PRAC reviewed data from the literature, clinical trials, and spontaneous case reports, some of which recorded a positive de-challenge. In view of a plausible mechanism of action, the PRAC concluded that there is reasonable evidence to suggest a causal relationship between exposure to leuprorelin and the development of IIH. As such, the product information** for depot formulations of leuprorelin has been updated to highlight that IIH has been reported with an unknown frequency in patients receiving leuprorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of leuprorelin should be considered.

* *Leuprorelin-containing depot medicines licensed in Ireland include Eligard, Leuprex, Lutrate and Prostap. Further details on leuprorelin-containing depot medicines are available at www.hpra.ie.*

** *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.*

Pholcodine-containing medicinal products – review of risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBA)

Pholcodine is licensed in Ireland as a single ingredient product to treat non-productive (dry) cough, and in combination with other active substances in preparations to treat the symptoms of common cold. Neuromuscular blocking agents (NMBAs) are licensed for adjunctive use in general anaesthesia to aid in intubation and as muscle relaxants, and include substances such as atracurium, cisatracurium, mivacurium, pancuronium, rocuronium, and suxamethonium.

The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has initiated a review of pholcodine-containing medicinal products* following concerns that their use may increase the risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBA).

The PRAC review was initiated following publication of preliminary results of a French multicentric case-control study (ALPHO)[1], which suggested that taking pholcodine up to 12 months before general anaesthesia may increase the risk of having an NMBA-related anaphylactic reaction. The ALPHO study was carried out as a condition to the marketing authorisations of pholcodine-containing medicines following a previous safety review in 2011. In 2021, while the ALPHO study was ongoing, the results of an Australian study[2] linked use of pholcodine to an increased risk of anaphylaxis to NMBAs. The PRAC considered that a causal relationship between pholcodine and cross-reactivity to NMBAs could not be ruled out and recommended updates to the product information** of all pholcodine-containing

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products (including fixed dose combinations), while awaiting the results of the ALPHO study, to warn patients and healthcare professionals that cross-reactivity leading to serious allergic reactions (anaphylaxis) has been reported between pholcodine and NMBAs. At this time, updates were also made to the product information to note that pholcodine is an opioid and addiction is observed with opioids as a class and, as such, these products should be used with caution in patients with a history of drug abuse.

The PRAC will now review the results of the ALPHO study together with all available data and assess their impact on the benefit-risk balance of pholcodine-containing medicines and issue a recommendation on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the EU. Further information can be found on the EMA website.

Advice to Healthcare Professionals

- Cross-reactivity leading to serious allergic reactions (anaphylaxis) has been reported between pholcodine and NMBAs.
- A precise at-risk period of time between the exposures of pholcodine and NMBAs has not been determined, and clinicians should be aware of this potential in case of future anaesthetic procedures involving NMBAs.

Key Message

The EMA's safety committee has initiated a review of pholcodine-containing medicinal products following concerns that their use may increase the risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBA).

In the interim, pending the outcome of the EMA review, the product information for pholcodine-containing medicinal products has been updated to warn that cross-reactivity leading to serious allergic reactions (anaphylaxis) has been reported between pholcodine and NMBAs.

Further information can be found on the EMA website.

* *Pholcodine-containing medicinal products licensed in Ireland include Pholcodex Oral Solution, and Day Nurse Capsules. Further details on pholcodine-containing medicines are available at www.hpra.ie and www.ema.europa.eu.*

** *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.*

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Product information updates recommended by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC)

The HPRA is highlighting a selection of recommendations, made by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), to update product information for medicines in clinical use. The PRAC, in which the HPRA participate, are responsible for assessing and monitoring the safety of medicines. Healthcare professionals (HCPs) are reminded to regularly check the HPRA or EMA websites for current product information concerning medicines they prescribe or dispense.

Clopidogrel: drug drug interaction (DDI) with morphine

Clopidogrel is a platelet aggregation inhibitor (P2Y12 inhibitor) indicated in adults for the secondary prevention of atherothrombotic events. In combination with acetylsalicylic acid, clopidogrel is indicated in patients with moderate to high-risk transient ischemic attack (TIA) or minor ischemic stroke (IS), in patients with acute coronary syndrome (ACS), and for prevention of atherothrombotic and thromboembolic events in atrial fibrillation.

- Morphine is often given as analgesic for severe pain, such as that resulting from acute coronary syndrome (ACS). A new warning in the product information for clopidogrel indicates that, as with other oral P2Y12 inhibitors, co-administration of opioid agonists such as morphine has the potential to delay and reduce the absorption of clopidogrel, presumably because of slowed gastric emptying. The clinical relevance is unknown. Healthcare professionals should consider the use of a parenteral antiplatelet agent in ACS patients requiring co-administration of morphine or other opioid agonists.
- Patients should be advised to inform their healthcare professional that they are being treated with clopidogrel, if they are to be prescribed any opioid.

Pegfilgrastim: Stevens-Johnson Syndrome can occur rarely

Pegfilgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

- A warning was added to product information for pegfilgrastim-containing medicines to note that Stevens-Johnson Syndrome (SJS), which can be life-threatening or fatal, can occur rarely (may affect up to 1 in 1,000 people). If SJS occurs in a patient being treated with pegfilgrastim then treatment should be stopped and not restarted again. The patient leaflet now outlines that SJS can appear as reddish target-like or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, and can be preceded by fever and flu-like symptoms. Advise patients to stop using pegfilgrastim if such symptoms develop, and to immediately contact their healthcare professional.

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Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Xalkori (crizotinib)	Vision disorders, including risk of severe visual loss, need for monitoring in paediatric patients
Imbruvica (ibrutinib)	New risk minimisation measures, including dose modification recommendations, due to the increased risk of serious cardiac events
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
Topamax (topiramate)	Ongoing EU review of potential risk of neurodevelopmental disorders in children exposed in utero
Rubraca (rucaparib)	Restriction of indication

Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at www.hpra.ie/report, which include an online report form.

All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted to the EMA's EudraVigilance database where they are available for analysis and to support early detection and monitoring of possible safety signals*.

Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

* *A privacy notice relating to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available on the HPRA website.*

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

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