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# HPRA DRUG SAFETY NEWSLETTER

112TH EDITION

## In this edition



## Fluoroquinolone antibiotics: Reminder about restrictions of use and risk of rare but serious long-lasting adverse reactions

Fluoroquinolones are a class of broad-spectrum antibiotics, which include the active substances ciprofloxacin, levofloxacin, and moxifloxacin*.

The European Medicines Agency (EMA) made strong recommendations to restrict the use of systemic and inhaled fluoroquinolones following an EU-wide review conducted in 2018 to evaluate the risk of serious and long-lasting (lasting months or years), disabling and potentially irreversible adverse reactions mainly affecting the musculoskeletal and nervous system. Because of the review conducted by EMA, the use of fluoroquinolone medicines was significantly restricted in 2019.

Serious adverse reactions can include tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, hallucinations, psychosis, sleep disorders and impaired senses (hearing, vision, taste and smell). Tendon damage (especially to Achilles tendon but other tendons can also be involved) can occur within 48 hours of commencing treatment or the effects can be delayed for several months after stopping treatment.

A recent EMA-funded study ("Impact of European Union Label Changes for Fluoroquinolone Containing Medicinal Products for Systemic and Inhalation Use" (EUPAS37856)) suggests that despite the new restrictions introduced in 2019, fluoroquinolones are still potentially being used outside the authorised indications. The study involved an analysis of prescribing rates for fluoroquinolones in six European healthcare databases (Belgium, France, Germany, the Netherlands, Spain, and the United Kingdom). Due to the limitations of the study, no definitive conclusions can be drawn.

However, the EMA are reminding healthcare professionals (HCPs) of the existing advice to limit the use of these medicines to their approved indications after a careful assessment of the benefits and risks for individual patients. The HPRA published a special edition Drug Safety Newsletter (Edition 91) highlighting all the primary outcomes from the 2018 EU-wide review, including recommendations for HCPs concerning fluoroquinolones and restrictions around their use.

A Direct Healthcare Professional Communication will also be issued outlining the restrictions on systemic and inhaled fluoroquinolone antibiotic use.

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## Advice to Healthcare Professionals

- Systemic and inhaled fluoroquinolones should NOT be prescribed for:
  - patients who have previously had serious adverse reactions with a quinolone or fluoroquinolone antibiotic.
  - non-severe or self-limiting infections (such as pharyngitis, tonsillitis and acute bronchitis);
  - mild to moderate infections (including uncomplicated cystitis, acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease (COPD), acute bacterial rhinosinusitis and acute otitis media) unless other antibiotics that are commonly recommended for these infections are considered inappropriate;
  - non-bacterial infections, e.g., non-bacterial (chronic) prostatitis;
  - preventing travellers' diarrhoea or recurrent lower urinary tract infections
- Systemic and inhaled fluoroquinolones are associated with very rare, serious, disabling, long-lasting and potentially irreversible adverse reactions. These products should be prescribed only for approved indications and after careful assessment of the benefits and risks in the individual patient.
- Special caution should be taken in patients who concurrently are treated with corticosteroids, in elderly, patients with renal impairment and patients who have undergone solid organ transplants, as the risk of fluoroquinolone-induced tendinitis and tendon rupture may be exacerbated in these patients.

## Key Message

- Findings of a study commissioned by EMA (EUPAS37856) suggest that fluoroquinolones are still potentially being used outside of their authorised indications.
- There are significant restrictions on the use of these medicines due to the risk of rare but long-lasting (up to months or years), serious, disabling and potentially irreversible adverse reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses).
- Healthcare professionals are reminded that the use of systemic and inhaled fluoroquinolone is restricted following an EU-wide review, previously communicated in HPRA Drug Safety Newsletter (Edition 91).

*** Fluoroquinolone antibiotics authorised in Ireland are:**

| ACTIVE INGREDIENT | BRAND AVAILABLE |
|---|---|
| Ciprofloxacin | Ciprofloxacin Krka, Ciprofloxacin Teva, Cifloxager, Cifox, Ciplox, Ciproxin, Profloxin, Truoxin IV |
| Levofloxacin | Levofloxacin Bluefish, Levofloxacin Fresenius Kabi Deutschland, Levofloxacin Hikma Farmaceutica, Levofloxacin Krka, Levofloxacin Baxter, Tavager, Tavanic |
| Delafloxacin | Quofenix |
| Moxifloxacin | Avelox, Moxifloxacin Fresenius Kabi |
| Further details available on www.hpra.ie and www.ema.europa.eu | |


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# Hydroxychloroquine: Risk of drug-induced liver injury

Hydroxychloroquine-containing medicines are authorised in Ireland for several treatment indications* and have biological actions similar to those of chloroquine, including, antimalarial and immunomodulatory properties.

Following a review of available data, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that product information** for hydroxychloroquine-containing medicines should be updated to include a warning on the risk of drug-induced liver injury (DILI).

Healthcare professionals are advised that serious cases of DILI have been reported during use of these medicines, including fatal cases. The types of DILI reported include hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure.

Risk factors may include pre-existing liver disease, or predisposing conditions such as uroporphyrinogen decarboxylase deficiency or concomitant hepatotoxic medications. Prompt clinical evaluation and measurement of liver function tests is recommended for patients who report symptoms that may indicate liver injury.

For patients with significant liver function abnormalities, the benefits and risks of continuing the treatment should be considered.

The package leaflet will also be updated with advice for patients, as appropriate.

## Key Message

- Serious cases of drug-induced liver injury (DILI) including fatal cases have been reported in patients receiving hydroxychloroquine-containing medicines.
- Risk factors include pre-existing liver disease, or predisposing conditions such as uroporphyrinogen decarboxylase deficiency or concomitant hepatotoxic medications.
- For patients who report symptoms that may indicate liver injury, prompt clinical evaluation and measurement of liver function tests is recommended.

* *Refer to product information of Plaquenil and Hydroxychloroquine Accord for authorised treatment indications.*

** *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 or www.ema.europa.eu.*


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# Tramadol-containing medicines: New warnings and precautions for use regarding sleep-related breathing disorders, adrenal insufficiency and serotonin syndrome

Tramadol is a centrally acting synthetic opioid analgesic indicated for the treatment of moderate to severe pain*.

Following a review of available data, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) recommended updates to warnings and precautions for these medicines. New warnings have been added to product information** in relation to sleep-related breathing disorders and adrenal insufficiency, as well as an update to information on serotonin syndrome.

## Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. The risk of CSA increases in a dose-dependent fashion. A decrease in opioid dosage should be considered in patients presenting with CSA.

## Adrenal insufficiency

Opioids may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy.

## Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol alone, as well as in combination with other serotonergic agents. Serotonin syndrome has been added to section 4.8 of the Summary of Product Characteristics (SmPC) as an adverse reaction of unknown frequency. If concomitant treatment with other serotonergic agents is clinically warranted, then careful observation of the patient is advised, particularly during treatment initiation and dose escalations. A dose reduction or discontinuation of therapy should be considered on the severity. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

Please refer to the SmPC for full details of warnings and precautions for use.

Healthcare professionals are reminded that tolerance, psychic and physical dependence may develop, especially after long-term use of tramadol containing medicines. In patients with a tendency to drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

## Key Message

- Tramadol-containing medicines can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. The risk of CSA increases in a dose-dependent fashion.
- Tramadol-containing medicines may occasionally cause reversible adrenal insufficiency, requiring monitoring and glucocorticoid replacement therapy.
- Serotonin syndrome has been reported in patients receiving tramadol-containing medicines alone or in combination with other serotonergic agents. If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

* *Further details on tramadol-containing 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 or www.ema.europa.eu.*


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# Product information updates recommended by Pharmacovigilance Risk Assessment Committee

The HPRA is highlighting a selection of recommendations, made by the 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. HCPs are reminded to regularly check the HPRA or EMA websites for current product information concerning medicines.

## Flucloxacillin-containing medicines: addition of a warning regarding hypokalaemia

- Product information has been updated to add a warning that hypokalemia (potentially life-threatening) can occur in patients treated with flucloxacillin-containing medicines, especially in high doses, with an unknown frequency.
- Hypokalaemia caused by flucloxacillin can be resistant to potassium supplementation and regular measurements of potassium levels are recommended during therapy with high doses of flucloxacillin.
- Consideration for this risk is also warranted when combining flucloxacillin with hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g., malnutrition, renal tubule disfunction).

## Ceftriaxone-containing medicines: addition of a warning regarding risk of encephalopathy

- Product information has been updated to reflect that encephalopathy can occur rarely with the use of ceftriaxone, particularly in elderly patients with severe renal impairment or central nervous system disorders.
- If ceftriaxone associated encephalopathy is suspected (e. g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

## Teicoplanin-containing medicines: updated warning on nephrotoxicity

- An existing warning in product information on renal toxicity has been expanded to reflect that nephrotoxicity has been reported in patients treated with teicoplanin. Careful monitoring of patients receiving the high loading dose regimen is recommended.
- This update follows the results of an observational post-authorisation safety study which reported a higher incidence of nephrotoxicity in patients who received the high loading dose regimen as compared to historical estimates based on literature reports in those receiving a low loading dose regimen.
- HCPs are reminded of the existing warning to carefully monitor patients with renal insufficiency and those receiving teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic potential, (e.g. aminoglycosides, colistin, amphotericin B, ciclosporin, and cisplatin).

## Xeljanz (tofacitinib): addition of warnings on the risks of hypoglycaemia in patients treated for diabetes and the risk of retinal venous thrombosis

- Product information has been updated to reflect that there have been reports of hypoglycaemia following initiation of tofacitinib in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.
- Patients and caregivers should be advised to tell their doctor if they have diabetes or are taking medicines to treat diabetes.
- In addition, product information has been updated to reflect that retinal venous thrombosis has been reported in patients treated with tofacitinib.
- Patients should be advised to promptly seek medical care in case they experience symptoms suggestive of retinal venous thrombosis e.g., acute changes to their eyesight (blurry vision, partial or complete loss of vision).


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

| PRODUCT | SAFETY ISSUE |
|---|---|
| Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) | Updated recommendations to minimise the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus kinase inhibitors (JAKi). |

## Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at http://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 the 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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