HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

FLUOROQUINOLONE ANTIBIOTICS – EU REVIEW ADVISES RESTRICTIONS FOR CERTAIN INFECTIONS AND WARNS OF RARE BUT SERIOUS LONG LASTING ADVERSE REACTIONS

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

A recent review by the European Medicine Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) of fluoroquinolone antibiotics (used by mouth, injection or inhalation) concluded that these agents have been associated with prolonged (months-years), serious, disabling and potentially irreversible adverse reactions. The review found that these rarely reported long lasting adverse reactions can involve several or multiple organ systems (musculoskeletal, peripheral and central nervous systems). The adverse reactions reported included well established risks such as tendonitis, tendon rupture, neuropsychiatric effects and neuropathies associated with paraesthesia. The review acknowledged however, that fluoroquinolones remain an important treatment option for some bacterial infections.

The PRAC held a public hearing on the topic in June 2018, where patient experiences with these medicines were heard. Patients who had experienced long-lasting serious adverse reactions particularly emphasised the impact on their lives and the importance of judicious use of these agents coupled with high quality information for patients on potential adverse reactions. Having considered the available evidence and patient experiences, the PRAC recommended in October 2018 that fluoroquinolone antibiotic use should be further restricted and the information provided to patients on potential adverse reactions should be expanded to emphasise, in particular, the possibility of persisting effects.

The PRAC review identified data from spontaneous reports and the scientific literature (which primarily consisted of analyses of case reports) on long lasting adverse reactions associated with fluoroquinolone use, and non-clinical mechanistic studies. A review of the EMA's EudraVigilance database identified 286 cases of serious adverse reactions reported as disabling and lasting 30 days or more without any confounding factors from across the EU over a 21-year period. While cumulative fluoroquinolone patient exposure data is not available for this time period, it is estimated that over 300 million daily doses of fluoroquinolone antibiotics are dispensed yearly[1*]. The primary disorders reported involved the musculoskeletal system and the nervous system, followed by neuropsychiatric disorders and eye disorders (visual impairment). Tendonitis and related reactions were the most commonly reported musculoskeletal effects, while paraesthesia was the most commonly reported nervous system effect.

Outcome of the review

- Fluoroquinolones are associated with prolonged serious, disabling and potentially irreversible adverse reactions.
- The use of fluoroquinolones has been restricted, which means that they should not be used:
  1. To treat mild or self-limiting conditions (e.g. pharyngitis, acute bronchitis),
  2. To treat non-bacterial infections,
  3. To prevent traveller's diarrhoea or to prevent recurring lower urinary tract infections,
  4. To treat mild or moderate bacterial infections unless other antibiotics commonly recommended for these infections are contraindicated.
- For patients with a serious infection (e.g. broncho-pulmonary infections in cystic fibrosis and complicated urinary tract infections) that is susceptible to treatment with these antibiotics, fluoroquinolones remain an important treatment choice.
- Fluoroquinolones should not be used to treat patients who have previously experienced serious adverse reactions while taking a fluoroquinolone.
- Fluoroquinolones should be used with caution in older patients, patients with renal impairment, patients with solid organ transplants and those treated concomitantly with corticosteroids, as the risk of some adverse reactions (tendonitis and tendon rupture) is increased in these patients.
- **Patients should be informed of the risks associated with fluoroquinolones prior to initiating treatment.**
- Fluoroquinolone treatment should be discontinued and alternative treatment should be considered at the first sign of tendonitis (e.g. painful swelling, inflammation).
- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for all fluoroquinolone antibiotics will be updated to reflect these recommendations following the issuance of a European Commission Decision (expected early 2019).
- Following the European Commission Decision in early 2019, a Direct Healthcare Professional Communication (DHPC) will be circulated to healthcare professionals by the Marketing Authorisation Holders (the companies that hold the licenses for these medicines), after approval by the HPRA.

Advice to Healthcare Professionals

- Fluoroquinolones are associated with prolonged (up to months or years), serious, disabling and potentially irreversible adverse reactions affecting several, sometimes multiple, systems, organ classes and senses.
- The adverse reactions include tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders and impaired 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.
- Patients who are older, have renal impairment or have had solid organ transplantation and those being treated with a corticosteroid are at higher risk of tendon damage. Concomitant treatment with a fluoroquinolone and a corticosteroid should be avoided.
- Fluoroquinolones should generally not be used in patients who have had serious adverse reactions associated with the use of quinolone or fluoroquinolone medicines.
- Patients should be advised of the risk of tendon damage and neuropathies and the potential long lasting and serious nature of these effects.
- Patients should be advised to read the package leaflet (PL) that accompanies their medicine.
- Fluoroquinolone treatment should be discontinued and alternative treatment should be considered at the first sign of tendonitis (e.g. painful swelling, inflammation) or symptoms of neuropathy such as pain, burning, tingling, numbness or weakness.

The PRAC recommendation has been forwarded by the EMA's Committee for Medicinal Products for Human Use (CHMP) to the European Commission for a legally binding decision.

Key Message

Fluoroquinolones are associated with serious adverse reactions affecting several, sometimes multiple, systems, organ classes and senses which, although rarely reported, may be prolonged, disabling and potentially irreversible.

Fluoroquinolone use has therefore been restricted as detailed above.

Patients who are older, have renal impairment or have had a solid organ transplant and those being treated with a corticosteroid are at higher risk of tendon damage. Concomitant treatment with a fluoroquinolone and a corticosteroid should be avoided.

Patients should be informed of the potentially serious and long lasting adverse reactions associated with fluoroquinolone antibiotics and advised to read the package leaflet that accompanies their medicine.

Patients should be advised to urgently seek medical advice at the first signs of these adverse reactions.

Healthcare professionals should discontinue fluoroquinolone treatment and consider alternative treatment at the first sign of tendonitis, neuropathy or other serious adverse reaction.

Any suspected adverse reactions associated with fluoroquinolone antibiotics should be reported to the HPRA via the usual methods (www.hpra.ie).

Risk of aortic aneurysm and dissection

As highlighted in the 90th edition of the HPRA Drug Safety Newsletter, in October 2018, a DHPC was circulated by the MAHs responsible for fluoroquinolones to relevant healthcare professionals regarding a new warning of the rare risk of aortic aneurysm and dissection associated with fluoroquinolones for systemic and inhalation use. In patients at risk of aortic aneurysm and dissection, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options.

*Fluoroquinolone antibiotics authorised in Ireland include:

Active Ingredient	Brands available
Ciprofloxacin	Ciprofloxacin, Cifloxager, Cifox, Ciplox, Ciproxin, Profloxin, Truoxin
Levofloxacin	Levofloxacin, Tavager, Tavanic
Ofloxacin	Tarivid
Moxifloxacin	Avelox, Moxifloxacin

Further details available on www.hpra.ie and www.ema.europa.eu

1: European Centre for Disease Prevention and Control. Antimicrobial consumption. In: ECDC. Annual epidemiological report for 2016. Stockholm: ECDC; 2018.
*Estimate based on a reported fluoroquinolone and quinolone daily dose of 1.7/1000 inhabitants per day in the community setting and 0.23/1000 inhabitants per day in the hospital setting and an EU population of approximately 500 million.