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Editorial

# A Call To Prevent Inappropriate Prescribing of Fluoroquinolones from the European Medicines Agency and the European Association of Urology Guidelines Panel for Urological Infections

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In March 2019, the European Commission implemented risk minimisation measures (RMMs) throughout the EU to prevent inappropriate prescribing of systemic and inhaled fluoroquinolones. This followed a comprehensive EU-wide review by the European Medicines Agency (EMA) that evaluated the impact of prolonged, disabling, and potentially irreversible serious adverse drug reactions (ADRs) on the benefit-risk balance of these antibiotics [1]. These very rare but serious ADRs primarily affect the musculoskeletal and nervous systems and can include tendonitis, tendon rupture, neuropsychiatric events, and neuropathies associated with paraesthesia. Tendonitis and tendon rupture, particularly of the Achilles tendon, can occur within 48 h of initiating fluoroquinolone treatment but can also be delayed for several months after discontinuation [1].

The RMMs implemented by the European Commission included (1) important restrictions on the therapeutic indications for fluoroquinolones, and (2) updates to the product information for both health care professionals and patients, with descriptions of these ADRs and precautions for fluoroquinolone use. In addition, a direct health care professional communication (DHPC) was disseminated to inform health care professionals accordingly [1].

At the time of the EU-wide review, systemic and inhaled fluoroquinolones were collectively approved in the EU for more than 100 indications, each with varying levels of granularity. The benefit-risk balance of each indication was evaluated and subsequently classified into one of four distinct categories on the basis of findings from the review [1].

The categorisation of urological indications is detailed in Table 1 [2]. In alignment with increasing clinical and regulatory concerns, the European Association of Urology (EAU) had already recommended against the use of fluoroquinolones for prostate biopsy prophylaxis and the treatment of uncomplicated cystitis in its 2020 guidelines on urological infections, recommendations that are also reiterated in the 2025 update [3].

The marketing authorisation for the quinolone antibiotics nalidixic acid, pipemidic acid, cinoxacin, and flumequine was also suspended given they did not retain any indication with a positive benefit-risk balance [1] at the time of the review.

Regarding precautions for use, fluoroquinolones should be avoided in patients who have previously experienced serious side effects with a fluoroquinolone or quinolone antibiotic. Special caution should also be exercised when prescribing fluoroquinolones for older patients, individuals with renal impairment, and patients who have received a solid organ transplant, as they may be at higher risk of tendon injury. Since administration of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided. Patients should be counselled to discontinue treatment at the first sign of adverse reactions affecting the musculoskeletal or nervous systems, and to contact their prescriber immediately [1].

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**Table 1Categorisation of urological indications for systemic fluoroquinolones**

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|---|
| **Category 1: Indications maintained (partly product-specific)** |
| o Complicated urinary tract infections/acute pyelonephritis |
| o (Acute) bacterial prostatitis, including cases due to susceptible *Neisseria gonorrhoeae* |
| o Epididymo-orchitis, including cases due to susceptible *N. gonorrhoeae* |
| o Urethritis and cervicitis (nongonococcal and/or gonococcal due to susceptible *N. gonorrhoeae)* |
| o Tuberculosis (in combination treatment, including urogenital infections) |
| o Treatment/prophylaxis for bacterial infections (in cases of fever) in patients with neutropenia |
| o Sepsis due to genitourinary infections → reworded to urosepsis |
| **Category 2: Indications restricted (to be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections)** |
| o Uncomplicated cystitis (ie, simple uncomplicated acute cystitis, acute cystitis in women, simple uncomplicated acute cystitis in premenopausal adult women, recurrent cystitis in women, and acute uncomplicated infection of the lower urinary tract [simple cystitis]) |
| **Category 3: Indications deleted** |
| o Prevention of exacerbations in women with recurring urinary tract infections (ie, prophylaxis for frequent recurrent urinary infection, long-term prophylaxis for recurrent urinary infections, prophylaxis for frequently repeating urinary tract infections, and prophylaxis for systemic urinary tract infections) |
| o Prevention of infection in surgical procedures (ie, prophylaxis after surgeries or interventions in the urogenital system, prophylaxis for recurrent urinary infections following transurethral surgery or transrectal prostate biopsy) |
| o Septicaemia*For pefloxacin only*: Acute and chronic prostatitis, including severe forms and acute uncomplicated pyelonephritis |
| **Category 4: Indications considered too broad and reworded according to current medical knowledge** |
| o Infections of the kidney, urinary tract and genitals → reworded into the indications above |

To evaluate the effectiveness of these RMMs, specifically with regard to changes in prescribing behaviour in the outpatient setting, an EMA-funded drug utilisation study (DUS) was commissioned as part of the EMA Pharmacovigilance Risk Assessment Committee strategy on measuring the impact of pharmacovigilance activities [4,5]. The DUS was a retrospective, population-based cohort study using primary care data from electronic health care records from six European countries between 2016 and 2021. The main objective was to evaluate the impact of regulatory actions to reduce prescribing of systemic and inhaled fluoroquinolones following implementation of the RMMs via statistical analysis of prescribing rates by indication [4].

The study findings showed that prescribing of systemic and inhaled fluoroquinolones in the primary care setting decreased over time in the six countries included in the study. In two countries, the UK and Germany, this decrease coincided with implementation of the RMMs in March 2019, specifically dissemination of the DHPC. In the other four countries—Belgium, France, Spain, and the Netherlands—a decrease in prescribing had commenced before implementation of the RMMs in March 2019. The incidence of use varied by country, ranging from 0.7 per 1000 persons per month in the UK to 8.0 per 1000 persons per month in Spain over all calendar years [4].

Overall, the magnitude of the decrease observed for all countries was limited, indicating that the RMMs had a modest impact in reducing the prescribing of systemic and inhaled fluoroquinolones in the primary care setting. While the study findings suggest that fluoroquinolones may still be prescribed outside the licensed indications recommended by the EMA, the study limitations precluded the ability to quantify the extent of such off-label use. These limitations included a high percentage of unknown indications, which ranged from approximately 38% to 84% across countries, and potential misclassification of cases concerning on- and off-label use [4]. The substantial proportion of prescriptions with unknown indications probably reflects limitations in health care data infrastructure, including inconsistent indication coding within electronic health records and the absence of mandatory diagnostic linkage in outpatient prescribing systems.

The translation of risk minimisation strategies into clinical practice remains a multifaceted and challenging process. Effective implementation of RMMs often depends on several inter-related factors, such as endorsement by professional societies (eg, via integration in evidence-based clinical guidelines), alignment with national reimbursement strategies, and continuous professional education, which may contribute to regional differences and explain the limited impact observed in the DUS.

During the evaluation of the DUS, the EMA noted the challenges associated with implementation of the RMMs, particularly with regard to changes in prescribing behaviour. The agency discussed the need to increase awareness among health care professionals given the instrumental role they play in ensuring successful implementation of RMMs. Consequently, another DHPC was disseminated in June 2023 to a broad range of health care professionals in the EU to remind them of the legally binding restrictions implemented in 2019 [6].

Throughout the evaluation of the DUS, the EMA liaised closely with representatives from patient organisations to ensure that their views and concerns regarding potential inappropriate prescribing of fluoroquinolones were incorporated into the decision-making process. Patient representatives emphasised the importance of raising awareness about the risk of these adverse reactions, particularly regarding the long latency (months to years) and of ensuring that health care professionals adequately counsel patients regarding these risks at the time of prescribing.

In 2024, the EMA conducted a thorough reassessment and evaluation of these serious ADRs to facilitate further characterisation, including elucidation of specific risk factors, pathological mechanisms, and clinical manifestations. While no new risk factors predisposing patients to these ADRs were identified, the EMA recommended that the product information for systemic and inhaled fluoroquinolones should be further updated to include anxiety, suicidal ideation, panic attack, neuralgia, and concentration impairment

as new aspects of these long-lasting and disabling serious ADRs [7].

In conclusion, while RMMs are designed and implemented by marketing authorisation holders as requested and overseen by medicines regulatory bodies, health care professionals play a crucial role in ensuring that they are integrated and adopted in practice. It is imperative that urologists adhere to guidelines to ensure appropriate prescribing of fluoroquinolones and counsel patients on these risks, including how to recognise the symptoms of these ADRs, to facilitate shared-decision making with patients.

***Conflicts of interest:*** The authors have nothing to disclose.

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