

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Germany:

Product Name	Quinolone- and fluoroquinolone-containing medicinal products
Active substance(s)	Nalidixic acid Pipemidic acid Cinoxacin Enoxacin Pefloxacin Lomefloxacin Ciprofloxacin Levofloxacin Ofloxacin Moxifloxacin Norfloxacin Prulifloxacin Rufloxacin Flumequin
Pharmaceutical form(s)	Pharmaceutical forms for systemic and inhalation use
Strength(s)	All
Route of administration(s)	Systemic and inhalation use
Marketing Authorisation Holder(s)	Various

Quinolones and the more potent fluoroquinolones, which target bacterial DNA gyrase (topoisomerase II) and topoisomerase IV, are important therapeutic options to treat serious life threatening bacterial infections.

In 2016, the FDA finalised a review of disabling and potentially permanent serious side effects of systemically applied fluoroquinolones that can occur together and can involve the peripheral and central nervous system as well as tendons, muscles and joints. Based on this review, the FDA recommended in May 2016 that "*serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.*"¹ The FDA safety review followed a thorough discussion of these safety issues at the FDA Advisory Committee meeting in November 2015². End of July 2016 the FDA approved changes to the labels of fluoroquinolones for systemic use based on this safety review³.

The safety review focussed on cases describing disabling symptoms referred to as "Fluoroquinolone-Associated Disability" (FQAD) and which must have adverse events reported from two or more of the following body systems:

- Musculoskeletal
- Senses (vision, hearing, etc.)
- Neuropsychiatric
- Skin
- Peripheral Nervous System
- Cardiovascular

and had to last 30 days or longer after stopping the fluoroquinolone. By applying these criteria 178 cases have been retrieved from a search in the FEARS database covering the period November 1, 1997 to May 30, 2015⁴.

Additionally, articles in peer-reviewed literature describing this constellation of disabling symptoms have been taken into account^{5,6}.

This specific safety concern of disabling and potentially permanent serious side effects affecting usually more than one body system has not yet been systematically evaluated for all affected medicinal products within previous EU regulatory procedures and, while the side effects are included in the product information of most of the medicinal products, the severity and the potential permanent effects are currently not fully addressed in the labelling of quinolones and fluoroquinolones that are authorised in the EU. An EU level review of both quinolones and fluoroquinolones would allow for an assessment of all the available evidence of disabling and potentially permanent serious side effects affecting the following body systems (musculoskeletal, senses [vision, hearing, etc.], neuropsychiatric, skin, peripheral nervous system, cardiovascular), in particular those that have been reported in the EU. . Quinolones should be included within the review in view of the plausibility that the safety concern may apply based on the high structural similarity with fluoroquinolones, the same mechanism of action (targeting bacterial DNA gyrase) and similar adverse effects like central nervous system adverse effects seen also in clinical trials⁷. This review should take into account the existing restrictions of indications in place for EU products.

Data from the German national database on adverse drug reactions has also revealed a number of such potential cases where serious adverse drug reactions lasted 30 days or longer after stopping the fluoroquinolone. Moreover, publications in the past years describe such long-term adverse events^{5,6}.

Considering the nature of disabling and potentially permanent serious side effects, such

review will enable an assessment of the need for adequate risk minimisation measures and the impact of this safety concern, if confirmed, on the overall benefit risk balance of quinolones and fluoroquinolones for systemic and inhalation use, especially in authorised indications for treatment of non-serious/non severe infections (such as uncomplicated urinary tract infections, acute bacterial sinusitis, acute exacerbation of chronic bronchitis).

In view of the above and the necessity to take an action at EU level, Germany considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation in accordance with Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CHMP on the basis of a recommendation of the PRAC.

Signed

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Date 1. February 2017

President of BfArM

¹ FDA May 12, 2016 [FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur](#)

² FDA November 5, 2015

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM467383.pdf>

³ FDA July 26, 2016

<http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm>

⁴ <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM472655.pdf>

⁵ Cohen JS. Peripheral neuropathy associated with fluoroquinolones. *Ann Pharmacother* 2001;35:1540-7

⁶ Golomb BA, Koslik HJ, Redd AJ. Fluoroquinolone-induced serious, persistent, multisystem adverse effects. *BMJ Case Rep* 2015 Oct 5. pii: bcr2015209821. doi: 10.1136/bcr-2015-209821.

⁷ Burt RA. Review of adverse reactions associated with cinoxacin and other drugs used to treat urinary tract infections. *Urology*. 1984 Jan;23(1):101-7.