



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 February 2017
EMA/PRAC/38617/2017

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for quinolones and fluoroquinolones containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1452

Quinsair EMEA/H/A-31/1452/C/002789/0010

INN/active substance(s): Nalidixic acid
Pipemidic acid
Cinoxacin
Enoxacin
Pefloxacin
Lomefloxacin
Ciprofloxacin
Levofloxacin
Ofloxacin
Moxifloxacin
Norfloxacin
Prulifloxacin
Rufloxacin
Flumequin



1. Background

This pharmacovigilance referral procedure under Article 31 of Directive 2001/83/EC focuses on the review of the impact of long-lasting, disabling and potentially irreversible adverse drug reactions (ADRs) on the benefit-risk balance of quinolones and fluoroquinolones for systemic and inhalation use.

In May 2016 the FDA conducted a review of disabling and potentially permanent serious side effects of systemically applied fluoroquinolones resulting in a restriction of use in less severe infections such as acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections, particularly in patients who have other treatment options. A similar approach was recently followed by Health Canada. While the ADRs are currently included in the EU product information, the persistence of these ADRs known to occur with quinolones and fluoroquinolones has not yet been systematically evaluated in the EU.

Considering the nature of these long-lasting, disabling and potentially irreversible ADRs, 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 considered that it is in the interest of the Union to refer the matter to the PRAC and requested on 1 February 2017 that it gives its recommendation as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

In the context of this referral the PRAC has adopted the list of questions to be addressed by the marketing authorisation holders MAH(s) as detailed in section 2.

In addition, the PRAC considered it necessary to perform a targeted Eudravigilance (EV) analysis of reports of adverse reactions related to the use of quinolones and fluoroquinolones containing medicinal products (with systemic and inhaled routes of administration), which have led to long-lasting, disabling and potentially irreversible effects. This analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs. This EV analysis will be provided to all MAHs together with the preliminary assessment reports.

2. Questions

The marketing authorisation holders MAH(s) are requested to address the following questions:

Question 1

Please provide any available evidence pointing to long-lasting, disabling and potentially irreversible adverse drug reactions (for example musculoskeletal impairment, peripheral neuropathy, neurological or psychiatric reactions, impairment of the senses) associated with the use of your product(s), including a review and discussion of clinical and epidemiological studies and literature relating to your product(s). As applicable, the methodology used should be provided.

Question 2

Please discuss possible mechanisms of long lasting, disabling and potentially irreversible adverse drug reactions, including a discussion on vasculitis, effects on mitochondria and mtDNA, effects on oxidative

stress, tendinocytes and matrix metalloproteinases, based on non-clinical and clinical published and unpublished data for your product(s).

Question 3

Please provide an assessment on the impact of occurrence of long lasting, disabling and potentially irreversible adverse drug reactions on the benefit-risk balance of your product(s) in the currently approved indication(s) in the EU. This assessment should take into account the characteristics of the clinical condition(s) for which the product is indicated.

Question 4

Please provide proposals and justifications with supportive evidence for any risk minimisation measures (including changes to the SmPC/PL) that may improve the benefit/risk balance of your product(s), and how their effectiveness should be monitored.

Please discuss whether additional risk minimisation measures (e.g. DHPC) are warranted in view of the above. In case a DHPC is considered warranted a DHPC proposal including a proposal for a communication plan should be provided.