EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quinolone- and fluoroquinolone-containing medicinal products

Procedure started

Under evaluation

PRAC recommendation

CHMP opinion

European Commission final decision

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CURRENT STATUS
European Commission final decision

Overview

Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics

On 15 November 2018, EMA finalised a review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics given by mouth, injection or inhalation. The review incorporated the views of patients, healthcare professionals and academics presented at EMA's public hearing on fluoroquinolone and quinolone antibiotics in June 2018.

EMA's human medicines committee (CHMP) endorsed the recommendations of EMA's safety committee (PRAC) and concluded that the marketing authorisation of medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended.

The CHMP confirmed that the use of the remaining fluoroquinolone antibiotics should be restricted. In addition, the prescribing information for healthcare professionals and information for patients will describe the disabling and potentially permanent side effects and advise patients to stop treatment with a fluoroquinolone antibiotic at the first sign of a side effect involving muscles, tendons or joints and the nervous system.

Restrictions on the use of fluoroquinolone antibiotics will mean that they should not be used:

- to treat infections that might get better without treatment or are not severe (such as throat infections);
- to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
- for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

Importantly, fluoroquinolones should generally be avoided in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic. They should be used with special caution in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided.

The CHMP opinion was forwarded to the European Commission, which issued a final legally binding decision on 14 February 2019 for Quinsair and on 11 March 2019 for other quinolone and fluoroquinolone antibiotics given by mouth and by injection, which is applicable in all EU countries. National authorities will enforce this decision for the fluoroquinolone and quinolone medicines authorised in their countries and they will also take other appropriate measures to promote the correct use of these antibiotics.

Information for patients

Fluoroquinolone medicines (which contain ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin) can cause long-

lasting, disabling and potentially permanent side effects involving tendons, muscles, joints and the nervous system.

- These serious side effects include inflamed or torn tendon, muscle pain or weakness, and joint pain or swelling, walking difficulty, feeling pins and needles, burning pain, tiredness, depression, problems with memory, sleeping, vision and hearing, and altered taste and smell.
- Tendon swelling and injury may occur within 2 days of starting treatment with a fluoroquinolone but may even occur several months after stopping treatment.
- Stop taking a fluoroquinolone medicine and contact your doctor at once in the following cases:
    - at the first sign of tendon injury, such as tendon pain or swelling – rest the painful area;
    - if you get pain, feel pins and needles, tingling, tickling, numbness or burning, or weakness especially in the legs or arms;
    - if you get swelling in the shoulder, arms or legs, have walking difficulty, feel tired or depressed or have problems with your memory or with sleeping or you notice changes with your vision, taste, smell or hearing. You and your doctor will decide if you can continue treatment or if you need to take another type of antibiotic.
- You may be more prone to joint pain or swelling or tendon damage if you are aged over 60 years, your kidneys do not work well or you have received organ transplantation.
- Speak with your doctor if you are taking a corticosteroid (medicines such as hydrocortisone and prednisolone) or need to have treatment with a corticosteroid. You may be especially prone to tendon damage if you are taking a corticosteroid and a fluoroquinolone medicine at the same time.
- You should not take a fluoroquinolone medicine if you have ever had a serious side effect with a fluoroquinolone or a quinolone medicine and you should speak with your doctor immediately.
- If you have any questions or concerns about your medicines, speak to your doctor or pharmacist.

Information for healthcare professionals

Fluoroquinolones are associated with prolonged (up to months or years), serious, disabling and potentially irreversible drug reactions affecting several, sometimes multiple, systems, organ classes and senses.

- The serious side effects 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 also other tendons) can occur within 48 hours of starting

fluoroquinolone treatment but the damage may be delayed 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.
- Fluoroquinolone treatment should be discontinued at the first sign of tendon pain or inflammation and patients should be advised to stop treatment with a fluoroquinolone and speak with the doctor in case of symptoms of neuropathy such as pain, burning, tingling, numbness or weakness so as to prevent development of potentially irreversible condition.
- Fluoroquinolones should generally not be used in patients who have had serious adverse reactions associated with the use of quinolone or fluoroquinolone medicines.
- Up-to-date summary of product characteristics should be consulted for authorised indications when considering treatment with a fluoroquinolone medicine. This is because the indications for these medicines have been restricted.
- The benefits and risks of fluoroquinolones will be monitored continuously and a drug utilisation study will evaluate the effectiveness of the new measures to reduce inappropriate use of fluoroquinolones by investigating changes in prescribing behaviour.

More about the medicine

Fluoroquinolones and quinolones are a class of broad-spectrum antibiotics that are active against bacteria of both Gram-negative and Gram-positive classes. Fluoroquinolones are of value in certain infections, including some life-threatening ones, where alternative antibiotics are not sufficiently effective.

The review covered medicines containing the following fluoroquinolone and quinolone antibiotics: cinoxacin, ciprofloxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, pefloxacin, pipemidic acid, prulifloxacin and rufloxacin.

The review concerned only medicines given systemically (by mouth or injection) and inhaled medicines.

More about the procedure

The review of fluoroquinolones and quinolones was initiated on 9 February 2017 at the request of the German medicines authority (BfArM), under Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines.

The final PRAC recommendations were adopted on 4 October 2018 and then sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency’s opinion. The CHMP opinion was forwarded to the European Commission, which issued a final legally binding decision on 14 February 2019

for Quinsair and on 11 March 2019 for other quinolone and fluoroquinolone antibiotics given by mouth and by injection, which is applicable in all EU Member States.

Quinolone and fluoroquinolone Article-31 referral - Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics (PDF/140.61 KB)

First published: 16/11/2018
Last updated: 19/03/2019
EMA/175398/2019

Available languages (22)

Key facts

Approved name

Quinolone- and fluoroquinolone-containing medicinal products

International non-proprietary name (INN) or common name

- nalidixic acid
- pipemidic acid
- cinoxacin
- enoxacin
- pefloxacin
- lomefloxacin
- ciprofloxacin
- levofloxacin
- ofloxacin
- moxifloxacin
- norfloxacin
- prulifloxacin
- rufloxacin
- flumequin

Associated names

Quinsair

Class

Quinolones and fluoroquinolones

Current status

European Commission final decision

Reference number

EMEA/H/A-31/1452

Type

Article 31 referrals

This type of referral is triggered when the interest of the Union is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines.

Authorisation model

Centrally and nationally authorised products (mixed)

Decision making model

PRAC-CHMP-EC

Procedure start date

09/02/2017

PRAC recommendation date

04/10/2018

CHMP opinion/CMDh position date

15/11/2018

EC decision date

11/03/2019

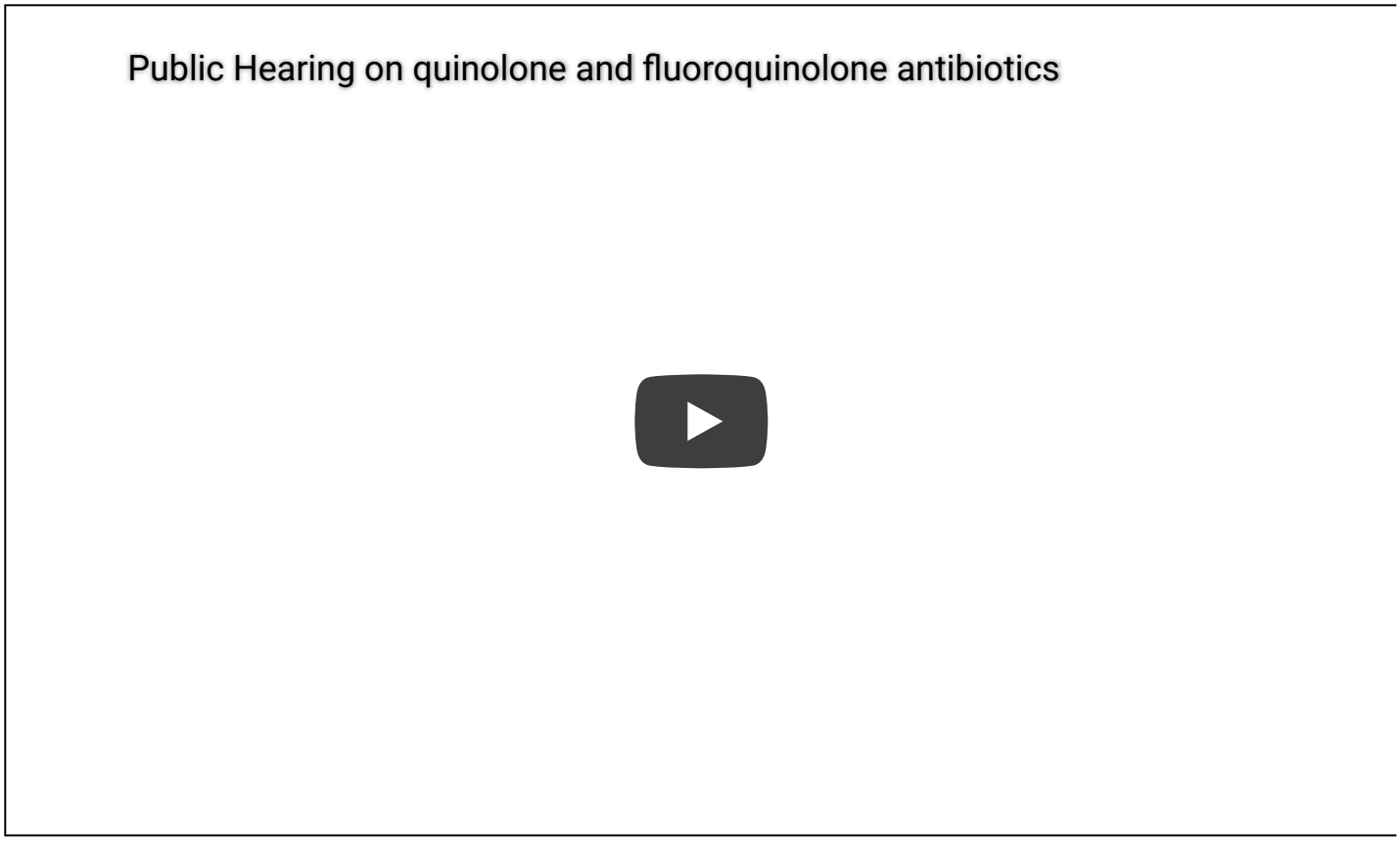
Outcome

Risk minimisation measures

Public hearing

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) held a public hearing on this topic on 13 June 2018 at the Agency's premises in London:

- Agenda and list of speakers
- Written interventions
- Summary report - available in all EU languages below



Speakers addressed the questions from the PRAC about the use of quinolones and fluoroquinolones:

- Summary of safety concerns and list of questions

More information

EMA selected speakers based on their **experience with these medicines** and how they plan to address the PRAC questions, whilst aiming to achieve a wide representation of stakeholders across the EU. The application deadline to participate in person was 30 April 2018.

EMA published detailed **guidance on how to participate** in a public hearing, including what to expect, how to register and how EMA selects speakers:

Public hearings - guidance for participants

The guidance describes the process and practical arrangements, including how to participate as a speaker or an observer.

EMA has also made an information video.

For more information on public hearings at EMA, see Public hearings.

The hearing will take place at the June PRAC meeting.

For additional information not available in the guidance, please email publichearings@ema.europa.eu .

All documents

Procedure started

Quinolone and fluoroquinolone Article-31 referral - Timetable for the procedure (PDF/76.22 KB)

First published: 10/02/2017
Last updated: 18/07/2018
EMA/PRAC/38618/2017 Rev. 6

Quinolone and fluoroquinolone Article-31 referral - PRAC list of questions (PDF/75.42 KB)

First published: 10/02/2017
Last updated: 10/02/2017
EMA/PRAC/38617/2017

Quinolone and fluoroquinolone Article-31 referral - Notification (PDF/218.18 KB)

First published: 10/02/2017
Last updated: 10/02/2017
EMA/85325/2017

Recommendation provided by Pharmacovigilance Risk Assessment Committee

Quinolone and fluoroquinolone Article-31 referral - PRAC recommends restrictions on use (PDF/175.92 KB)

First published: 05/10/2018
EMA/668915/2018

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Quinolone and fluoroquinolone Article-31 referral - Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics (PDF/140.61 KB)

First published: 16/11/2018

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Available languages (22)

Quinolone and fluoroquinolone Article-31 referral - Annex IV (PDF/16.71 KB)

First published: 19/03/2019

Available languages (22)

Quinolone and fluoroquinolone Article-31 referral - Annex II (PDF/176.91 KB)

First published: 19/03/2019

Available languages (22)

Quinolone and fluoroquinolone Article-31 referral - Assessment report (PDF/1.06 MB)

Adopted

First published: 19/03/2019
EMA/818158/2018

Quinolone and fluoroquinolone Article-31 referral - Annex III (PDF/287.92 KB)

First published: 19/03/2019

Available languages (24)

Quinolone and fluoroquinolone Article-31 referral - Annex I (PDF/3.37 MB)

First published: 13/02/2017
Last updated: 19/03/2019

Available languages (24)

Description of documents published

Please note that some of the listed documents apply only to certain procedures.

- Overview - lay-language summary of the stage of the procedure

- Notification – a letter from a Member State, the European Commission or the marketing authorisation holder requesting the initiation of the procedure
- Scientific background – further background information from the triggering Member State on the issues leading to the initiation of the procedure (if applicable)
- List of questions – questions agreed by the Committee requesting further information from the marketing authorisation holder(s) / applicant(s) to evaluate the issues identified
- Timetable for the procedure – agreed timeframe to respond to the list of questions, to assess the issues and to adopt a conclusion
- List of medicines concerned by the procedure – medicine(s) / active substance(s) concerned, and marketing authorisation holder(s) / applicant(s)
- List of questions to be addressed by the stakeholders – call for data to be submitted by stakeholders (e.g. healthcare professionals, patient organisations, individual patients) (if applicable)
- Stakeholder submission form – form to be used by stakeholders to submit data (if applicable)
- Scientific conclusions – scientific conclusions of the PRAC and/or CHMP and/or CMDh
- Assessment report – PRAC or CHMP assessment and conclusions on the issues investigated, including divergent positions (if applicable)
- Divergent positions – divergent positions of the CHMP or CMDh members for pharmacovigilance procedures (if applicable)
- Changes to the summary of product characteristics, labelling and package leaflet (amended sections or fully revised version) (if applicable)
- Condition(s) to the marketing authorisation(s) – condition(s) for the safe and effective use of the medicine(s) (if applicable)
- Condition for lifting the suspension – condition to be fulfilled for the suspension of the marketing authorisation(s) to be lifted (if applicable)
- Timetable for implementation of CMDh position – agreed timeframe to submit and finalise the variation(s) implementing the outcome of the procedure (if applicable)

Note that older documents may have different titles.

News

- Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics
  16/11/2018
- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 12-15 November 2018
  16/11/2018
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 1-4 October 2018

05/10/2018

- Fluoroquinolone and quinolone antibiotics: PRAC recommends new restrictions on use following review of disabling and potentially long-lasting side effects
  05/10/2018
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 3-6 September 2018
  07/09/2018
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 9-12 July 2018
  13/07/2018
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 11-14 June 2018
  15/06/2018
- Public hearing on quinolones and fluoroquinolones: 23 speakers from 11 EU countries to share experience
  07/06/2018
- Public hearing on 13 June 2018
  09/04/2018
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5-8 March 2018
  09/03/2018
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 January 2018
  12/01/2018
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 6-9 February 2017
  10/02/2017

Related content

- Quinsair: EPAR

Video recording of public hearing

The PRAC held a public hearing on this topic on 13 June 2018, at its meeting of 11-14 June. For more information, click on the 'Public hearing' tab on this page.

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