

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

Safety Announcement

[07-26-2016] The U.S. Food and Drug Administration (FDA) approved changes to the labels of fluoroquinolone antibacterial drugs for systemic use (i.e., taken by mouth or by injection). These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, we revised the *Boxed Warning*, FDA’s strongest warning, to address these serious safety issues. We also added a new warning and updated other parts of the drug label, including the patient Medication Guide.

We have determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.

Patients must contact your health care professional immediately if you experience any serious side effects while taking your fluoroquinolone medicine. Some signs and symptoms of serious side effects include unusual joint or tendon pain, muscle weakness, a “pins and needles” tingling or pricking sensation, numbness in the arms or legs, confusion, and hallucinations. Talk with your health care professional if you have any questions or concerns (see **List of Serious Side Effects from Fluoroquinolones**).

Health care professionals should not prescribe systemic fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risks outweigh the benefits in these patients. Stop fluoroquinolone treatment immediately if a patient reports serious side effects, and switch to a non-fluoroquinolone antibacterial drug to complete the patient’s treatment course (see **List of Currently Available FDA-approved Fluoroquinolones for Systemic Use**).

Fluoroquinolones are antibiotic medicines that work by killing or stopping the growth of bacteria that can cause illness. They are FDA-approved to prevent or treat certain serious bacterial infections.

The labels of fluoroquinolone medicines already have a *Boxed Warning* for tendinitis, tendon rupture, and worsening of myasthenia gravis. The labels also include warnings about the risks of

peripheral neuropathy and central nervous system effects. Other serious risks associated with fluoroquinolones are described in the labels, such as cardiac, dermatologic, and hypersensitivity reactions. After FDA's 2013 review that led to the additional warning that peripheral neuropathy may be irreversible, FDA evaluated post-marketing reports* of apparently healthy patients who experienced disabling and potentially permanent side effects involving two or more body systems after being treated with a systemic fluoroquinolone (see **Data Summary**). We evaluated only reports submitted to FDA, so there are likely additional cases of which we are unaware. The side effects occurred within hours to weeks after starting the fluoroquinolone, and at the time we received the reports, the side effects had continued for an average of 14 months to as long as 9 years after stopping the medicines. Several cases reported that some side effects stopped or improved after discontinuation of the medicine; others reported the side effects worsened or continued.

We previously communicated about these safety issues associated with fluoroquinolones in [May 2016](#). Additional communications about related safety issues associated with fluoroquinolones occurred in [August 2013](#) (peripheral neuropathy) and [July 2008](#) (tendinitis and tendon rupture). The safety issues described in this Drug Safety Communication were also discussed at an [FDA Advisory Committee meeting](#) in November 2015.

In addition to updating information in the *Boxed Warning*, we are also including information about these safety issues in the *Warnings and Precautions* section of the label. The *Indications and Usage* section contains new limitation-of-use statements to reserve fluoroquinolones for patients who do not have other available treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI). The patient Medication Guide that is required to be given to the patient with each fluoroquinolone prescription describes the safety issues associated with these medicines. We are continuing to assess safety issues with fluoroquinolones as part of FDA's usual ongoing review of drugs and will update the public if additional actions are needed.

We urge health care professionals and patients to report side effects involving fluoroquinolone antibacterials and other drugs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

List of Currently Available FDA-approved [Fluoroquinolones](#) for Systemic Use

Brand Name	Active Ingredient
Avelox	moxifloxacin ⁺
Cipro	ciprofloxacin ⁺
Cipro extended-release [±]	ciprofloxacin extended-release
Factive	gemifloxacin ⁺
Levaquin	levofloxacin ⁺
Ofloxacin (Generic brand) [±]	ofloxacin

⁺ available as brand and generic

[±] available only as generic

*The cases were reported to the [FDA Adverse Event Reporting System \(FAERS\)](#).

Facts about the Fluoroquinolone Drug Class

- Fluoroquinolones are a class of antibacterial drugs approved to treat or prevent certain bacterial infections
- The benefits of fluoroquinolone drugs outweigh the risks for treatment of serious infections caused by fluoroquinolone-susceptible bacteria, such as pneumonia or intra-abdominal infections.
- For patients who have other treatment options available for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections, the risks of fluoroquinolone drugs outweigh the benefits.
- Fluoroquinolones work by killing or stopping the growth of bacteria that can cause illness. Like other antibacterial drugs, fluoroquinolones do not treat viral infections such as colds, the flu, or bronchitis in otherwise healthy persons.
- Common side effects include nausea, diarrhea, headache, dizziness, lightheadedness, or trouble sleeping.
- In 2014, approximately 22 million unique patients received a dispensed prescription for a selected oral fluoroquinolone (e.g. ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin) from U.S. outpatient retail pharmacies.¹

Additional Information for Patients

- Fluoroquinolone antibiotic medicines are associated with disabling and potentially permanent serious side effects that can occur together in the same patient and should not be used to treat certain uncomplicated infections. These uncomplicated infections include acute bacterial sinusitis (ABS), acute worsening of bacterial chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI).
- These side effects can involve the tendons, muscles, joints, nerves, and central nervous system, and can occur within hours to weeks after starting a fluoroquinolone medicine.
- FDA has updated the *Boxed Warning* in the labels, added new warnings, and has revised the patient Medication Guide of all fluoroquinolone antibiotics.
- Contact your health care professional immediately if you experience any serious side effects while you are taking your fluoroquinolone medicine.
- Before starting a new fluoroquinolone medicine, inform your health care professional if you have previously experienced any serious side effects with another antibiotic.
- Serious side effects involving the tendons, muscles, joints and nerves include:
 - Swelling or inflammation of the tendons
 - Tendon rupture
 - Tingling or pricking sensation (“pins and needles”)
 - Numbness in arms or legs
 - Muscle pain
 - Muscle weakness
 - Joint pain
 - Joint swelling
- Serious central nervous system side effects include:
 - Depression

- Hallucinations
 - Suicidal thoughts
 - Confusion
 - Anxiety
- Other side effects include:
 - Abnormally rapid or irregular heart beat
 - Ringing or buzzing in the ears
 - Vision problems
 - Skin rash
 - Sensitivity of skin to sunlight
 - Headache
 - Trouble falling asleep
 - Fatigue
- Read the patient [Medication Guide](#) you receive with your fluoroquinolone antibiotic prescriptions, which explains the benefits and risks of the medicine.
- Talk to your health care professional if you have questions or concerns about fluoroquinolone antibiotic medicines.
- We communicated safety information associated with fluoroquinolones in [May 2016](#), [August 2013](#), and [July 2008](#).
- Report side effects from a fluoroquinolone or any drug to your health care professional and the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA has approved label changes that reserve the use of fluoroquinolone antibacterial medicines when treating acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) for patients who do not have alternative treatment options.
- FDA has also updated the *Boxed Warning* and the *Warnings and Precautions* sections of the labels and revised the patient Medication Guide of the fluoroquinolone drug class to describe the serious risk of multiple disabling and potentially irreversible adverse reactions that can occur together.
- These adverse reactions primarily include tendinitis and tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects.
- The adverse reactions can occur within hours to weeks after starting treatment with a fluoroquinolone medicine.
- Discontinue the fluoroquinolone medicine immediately at the first signs or symptoms of any serious adverse reaction.
- Avoid fluoroquinolones in patients who have previously experienced serious adverse reactions associated with fluoroquinolones.
- Serious Adverse reactions of the musculoskeletal system and peripheral nervous system include:
 - Tendinitis/Tendon rupture
 - Muscle pain

- Muscle weakness
 - Joint pain
 - Joint swelling
 - Peripheral Neuropathy
- Serious Central nervous system effects include:
 - Psychosis
 - Anxiety
 - Insomnia
 - Depression
 - Hallucinations
 - Suicidal thoughts
 - Confusion
- Other adverse reactions include:
 - Exacerbation of myasthenia gravis
 - Prolongation of the QT interval
 - Hypersensitivity reactions/anaphylaxis
 - Photosensitivity/phototoxicity
 - Blood glucose disturbances
 - *Clostridium difficile*-associated diarrhea
- Encourage patients to read the [Medication Guide](#) that they receive with their fluoroquinolone prescriptions.
- FDA convened a public advisory committee meeting in [November 2015](#) to discuss the risks and benefits of fluoroquinolone antibacterial medicines for the treatment of ABS, ABECB, and uncomplicated UTI. We also communicated safety information associated with fluoroquinolones in [May 2016](#), [August 2013](#), and [July 2008](#).
- Report adverse reactions involving a fluoroquinolone or any drug to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Data Summary

FDA completed a review of the results of placebo-controlled clinical trials of various antibacterial drugs conducted in patients that have acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI). Many of the trials were conducted in recent years and some ABS and ABECB trials did not show a benefit over placebo. Some trials showed a treatment benefit for ABS and ABECB, and most trials showed a treatment benefit for uncomplicated UTI, but many patients who received a placebo had clinical resolution of their infection. As part of our usual safety monitoring, we evaluated postmarketing reports of adverse reactions associated with fluoroquinolone antibacterial drugs in order to re-evaluate the risks and benefits of fluoroquinolone antibacterial drugs for treatment of these conditions.

A search of the [FDA Adverse Event Reporting System \(FAERS\)](#) database from November 1997 to May 2015, identified 178 U.S. cases of apparently healthy patients who took an oral fluoroquinolone to treat ABS, ABECB, or uncomplicated UTIs and developed disabling and potentially irreversible adverse reactions that appeared as a constellation of symptoms. Because it was difficult to clearly ascertain whether the report was for treatment of two of these

indications, ABECB or uncomplicated UTI, the search was broadened to include the indications “bronchitis” and “urinary tract infections” in addition to ABS, ABECB, and uncomplicated UTI. Only patients who reported adverse reactions lasting longer than a month and involving two or more body systems (e.g., musculoskeletal, peripheral nervous system, neuropsychiatric, senses, cardiovascular, and skin) were included in the evaluation. The majority of the adverse reactions primarily affected the musculoskeletal system, peripheral nervous system, and central nervous system.

The majority of cases (74%) were in patients 30 to 59 years. Many patients described how seriously the disability impacted their lives, including job loss and the resulting lack of health insurance, large medical bills, financial problems, and family tension or dissolution.

The mean duration of the disabling adverse reactions at the time the report was received by FDA was 14 months, with the longest duration reported 9 years. Several cases reported that selected adverse reactions either resolved or improved; other cases reported that the reactions got worse or continued. It is possible these adverse reactions may be permanent.

Long-term pain of any kind was the most commonly reported symptom, with 97% of all cases reporting pain associated with the musculoskeletal adverse reactions. The ongoing neuropsychiatric adverse reactions were reported to be distressing, affecting employment and quality of life.

References

1. IMS Health, Vector One®: Total Patient Tracker (TPT), Y2014, Extracted AUG2015.

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Factive	gemifloxacin ⁺
Levaquin	levofloxacin ⁺
Ofloxacin (generic brand) [±]	ofloxacin

⁺ available as brand and generic

[±] available only as generic

List of Serious Side Effects from Fluoroquinolones for Systemic use

Musculoskeletal and Peripheral Nervous System	Central Nervous System
Tendinitis	Anxiety
Tendon rupture	Depression
Numbness or tingling or pricking sensation “pins and needles” in arms or legs	Hallucinations

Muscle weakness	Suicidal Thoughts
Muscle pain	Confusion
Joint pain	
Joint swelling	
Other Body Systems	
Worsening of myasthenia gravis	
Skin rash	
Sunburn	
Abnormal, rapid or strong heart beat	
Severe diarrhea	

Related Information

The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective

<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm>

FDA updates warnings for fluoroquinolone antibiotics

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm513183.htm>

FDA approves safety labeling changes for fluoroquinolones

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm500325.htm>

Thinking it Through: Managing the Benefits and Risks of Medicines

<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143558.htm>

Advisory Committees: Critical to the FDA's Product Review Process

<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143538.htm>