DRUG REGULATORY AUTHORITY OF PAKISTAN
DIVISION OF PHARMACY SERVICES
MINISTRY OF NATIONAL HEALTH SERVICES, REGULATIONS & COORDINATION
ISLAMABAD
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FLOUROQUINOLONES

Drug Regulatory Authority of Pakistan requires label changes to reserve the use of fluoroquinolones antibacterial medicines for use in patients who have no other treatment options available for acute bacterial sinusitis, acute exacerbation of chronic bronchitis and uncomplicated urinary tract infection and to warn of risks of disabling side effects involving tendons, muscles, joints, nerves and the central nervous system associated with the use of all systemic Fluoroquinolones.

Fluoroquinolones have risks and benefits that should be considered very carefully, it's important that both health care providers and patients are aware of both the risks and benefit of fluoroquinolones and **make an informed decision about their use with caution**.

Fluoroquinolones are antibiotics that kill or stop the growth of bacteria. While these drugs are effective in treating bacterial infection, FDA safety review found both oral and injectable fluoroquinolones area associated with disabling side effects involving tendons, muscles, joints, nerves and the central nervous system. These side effects can occur hours to weeks after exposure to fluoroquinolones and may potentially be permanent.

Because the risk of these serious side effects generally outweighs the benefits for patients with acute bacterial sinusitis, acute exacerbation of chronic bronchitis and uncomplicated urinary tract infections, the FDA has determined that fluoroquinolones should be reserved for use in patients with these conditions who have no alternative treatment options. For some serious bacterial infections, including anthrax, plague and bacterial pneumonia among others, the benefits of fluoroquinolones outweigh the risks and it is appropriate for them to remain available as therapeutic option.

Drug Registration Board, Drug Regulatory Authority of Pakistan have already approved fluoroquinolones (systemic) preparation i.e. injectable and oral include levofloxacin, ciprofloxacin, moxifloxacin, ofloxacin, norfloxacin and gemifloxacin. Keeping in view the potential risk of serious adverse reactions including tendinitis and tendon rupture, peripheral

neuropathy, and central nervous system effects the labelling changes involved an inclusion of Boxed warning and revisions to the warning and precaution section of the label about the risk of disabling and potentially irreversible adverse reaction that can occur together. Systemic fluoroquinolones may exacerbate muscles weakness in patients with myasthenia gravis. The label also contains new limitation-of-use statement to reserve fluoroquinolones for patients who do not have other available treatment option for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infection.

DRAP has required the Drug Labels/package inserts and all other literature of all systemic fluoroquinolones antibacterial drugs designed to promote the drug and provide information to Patient or health care provider be updated to better describe the potentially irreversible serious adverse reactions including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects. Systemic fluoroquinolones may exacerbate muscles weakness in patients with myasthenia gravis.

Peripheral Neuropathy: - It is a nerve disorder occurring in the arms or legs. Symptoms include pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature, or the sense of body position. It can occur at any time during treatment with Fluoroquinolones and can last for months to years after the drug is stopped and may be permanent in some patients. This serious nerve damage is potentially caused by products containing Fluoroquinolones in oral or injectable dosage form and may occur soon after these drugs are administered.

Patients using Fluoroquinolones who develop any symptoms of peripheral neuropathy (arms or legs pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature) should tell their health care professionals right away.

If a patient develops symptoms of peripheral neuropathy, the doctors shall stop the Fluoroquinolones antibiotics, and the patient should be switched to another, non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a Fluoroquinolones outweighs the risk. Systemic fluoroquinolones shall be avoided in patients who have previously experienced peripheral neuropathy.

Tendinitis, Tendon Rupture: - Systemic fluoroquinolones have been known to cause serious tendinitis and even tendon rupture. Serious tendinopathies including tendon rupture have occurred in patients taking fluoroquinolone antibiotics. The Achilles tendon (tendons running along the back side of ankle) is most frequently involved but the tendons of the rotator cuff (shoulder); biceps (upper arm) and hand have been affected. Multiple tendons may be involved and significant disabilities can result. Tendinitis or tendon rupture can occur, within hours or days of starting fluoroquinolones antibiotics, or as long as several months after completion of fluoroquinolones therapy. Tendinitis and tendon rupture can occur bilaterally.

The risk of tendonitis and tendon rupture is increased in elderly patients, patients on corticosteroids (prednisone, dexamethasone, prednisilone or methyl prednisolone) and in patients with kidney, heart or lung transplants. However, this complication has also occurred in people who do not fit into any of these categories.

At the first sign of pain or inflammation of a tendon, patients shall stop taking the medication and contact their doctor immediately. Refrain from exercise or excessive use of the joint until the diagnosis of tendonitis can be excluded.

Doctors shall stop the fluoroquinolones antibiotics immediately, if patients experienced any sign or symptoms of tendinitis or tendon rupture, and shall avoid fluoroquinolones antibiotics in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture.

Worsening of symptoms of Myasthenia Gravis/ exacerbation of Myasthenia Gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolones use in persons with myasthenia gravis.

Patients who have myasthenia gravis and experience worsening of muscles weakness and breathing problems shall report immediately to their doctors.

Doctor shall avoid the use of fluoroquinolones in patients who have known history of myasthenia gravis.

Limitation/Restriction of Use statement

"Fluoroquinolones shall be reserve for use in patients who have no other treatment options available for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI)".

Systemic Fluoroquinolones are associated with disabling and potentially permanent side effects of tendons, muscles, joints, nerve, and central nervous system that can occur together in the same patient. These mentioned side effects/Risks associated with use of fluoroquinolones outweigh its benefits in patients who have acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI); hence it shall be the last choice in these conditions. The benefits of fluoroquinolones drugs outweigh the risk for treatment of serious infections caused by fluoroquinolones-susceptible bacteria, such as pneumonia or intra-abdominal infections; hence it is appropriate for them to remain available as therapeutic option.

Information for Patients

Patients must contact their health care professional immediately if they experience any serious effects during their treatment with fluoroquinolones. Some sign and symptoms of serious side effects include unusual joints or tendon pain, muscle weakness, a "pin and needle tingling or pricking sensation, numbness in arms or legs, confusion, hallucination.

Fluoroquinolones 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, acute worsening of bacterial chronic bronchitis, and uncomplicated urinary tract infection.

Before starting a new fluoroquinolones medicine, patient shall inform their doctor if they have previously experienced any serious side effect with another antibiotic or even fluoroquinolones.

Serious side effects involving the tendons, muscles, joints and nerve include:

- Swelling or inflammation of the tendons.
- Tendon rupture
- Tingling or pricking sensation (pins and needles)
- Joint swelling
- Muscles pain
- Join pain
- Numbness in arm or legs

Serious central nervous system side effects include:

- Hallucination
- Confusion
- Suicidal thought
- Anxiety
- Depression

Other side effects include:

- Ringing or buzzing in the ears
- Headache
- Abnormally rapid or irregular heart beat
- Skin rash
- Fatigue
- Vision problem
- Trouble falling asleep

Information for Doctors

- Drug Regulatory Authority of Pakistan (DRAP) require to update the label/ package inserts of all systemic fluoroquinolones to describe the serious risk of multiple disabling and potentially irreversible adverse reaction that can occur together.
- These adverse reactions primarily include tendinitis and tendon rupture, muscle pain, muscle weakness, joint pain, peripheral neuropathy and central nervous system effects.
- These adverse reactions can occur within hours to weeks after starting treatment with systemic fluoroquinolones.
- Doctor 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 fluoroquinolones treatment immediately if a patient reports serious side effects, and switch to a non-fluoroquinolone antibacterial drug to complete the patient's treatment course.
- Avoid fluoroquinolones in patients who have previously experience serious adverse reaction associated with fluoroquinolones and patients who have known history of myasthenia gravis.

- 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
    - Tremors
- Other Adverse Reaction include:
    - Exacerbation of Myasthenia gravis.

As per WHO newsletter no.3/2016 and intimation letter by M/S Bayer Pakistan Limited regarding fluoroquinolones label update and restriction of use by the FDA, case of was presented in the 263rd meeting of Drug Registration Board Meeting Drug held on 29th & 30th November, 2016 which decided to update the label/ package inserts of systemic fluoroquinolones as per Rule .30 (10) [a] of drug licensing, registration and advertising rules 1976.

The format of Boxed Warning in the package inserts of all systemic fluoroquinolones shall be as under:

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS.

- Fluoroquinolones, including (generic name), have been associated with disabling and potentially irreversible serious adverse reaction that have occurred together, including:
  - Tendinitis and tendon rupture
  - Peripheral Neuropathy
  - Central nervous system effects

Discontinue [Generic Name of Fluoroquinolone] immediately and avoid the use of Fluoroquinolones, including [Generic Name of Fluoroquinolone] in patients who experience any of these serious adverse reactions.

- Fluoroquinolones, including [Generic Name] may exacerbate muscle weakness in patients with myasthenia gravis. Avoid [Generic Name of Fluoroquinolone] in patients with known history of myasthenia gravis.
- As fluoroquinolones, including [Generic Name] have been associated with serious adverse reactions, reserve [Generic Name] for use in patients who have no alternative treatment options for the following indications:
  - Acute exacerbation of chronic bronchitis
  - Acute sinusitis
  - Acute uncomplicated cystitis *(not for Ciprofloxacin injection and Moxifloxacin infusion &tablets*)

The labels or packing of systemic fluoroquinolones shall bear the following words (IN RED INK):

WARNING:
See the Package Insert

DRAP will continue to keep eye on ongoing global evaluation process regarding safety of drugs in the fluoroquinolone class and will communicate with the public again if additional information becomes available.

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Further Reference.

1. **Food and Drug Administration (FDA), USA.**