

ABRIDGED PRESCRIBING INFORMATION FOR MEDICAL PROFESSIONALS

Uzaril

(Ciprofloxacin HCl USP)

یوزاریل
(سیپروفلوکساسن ہائیڈروکلورائیڈ)

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS
See full prescribing information for complete boxed warning. Fluoroquinolones including Ciprofloxacin have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together:

- Tendinitis and tendon rupture
 - Peripheral neuropathy
 - Central nervous system effects
- Discontinue Ciprofloxacin immediately and avoid the use of fluoroquinolones including Ciprofloxacin in patients who experience any of these serious adverse reactions.
- Fluoroquinolones including Ciprofloxacin may exacerbate muscle weakness in patients with myasthenia gravis. Avoid Ciprofloxacin in patients with known history of myasthenia gravis.
 - Because fluoroquinolones including Ciprofloxacin have been associated with serious adverse reactions reserve Ciprofloxacin for use in patients who have no alternative treatment options for the following indications:
- Acute exacerbation of chronic bronchitis
 - Acute uncomplicated cystitis
 - Acute sinusitis

COMPOSITION

Each **Uzaril** 250mg film coated tablet contains Ciprofloxacin HCl equivalent to Ciprofloxacin 250mg.
Each **Uzaril** 500mg film coated tablet contains Ciprofloxacin HCl equivalent to Ciprofloxacin 500mg.

DESCRIPTION

Ciprofloxacin, is synthetic antimicrobial agent for oral administration. Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents.

CLINICAL PHARMACOLOGY

Mechanism of Action: As a fluoroquinolone antibacterial agent, the bactericidal action of Ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Pharmacokinetics: Absorption: The absolute bioavailability of Ciprofloxacin when given as an oral tablet is approximately 70% with no substantial loss by first pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Serum concentrations increase proportionately with doses up to 1000 mg.

Food: When Ciprofloxacin is given concomitantly with food, there is a delay in the absorption of the drug resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour. Avoid concomitant administration of Ciprofloxacin with dairy products (like milk or yogurt) or calcium-fortified juices alone since decreased absorption is possible, however, Ciprofloxacin may be taken with a meal that contains these products.

Distribution: The binding of Ciprofloxacin to serum proteins is 20% to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs. After oral administration, Ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF), however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Metabolism: Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged Ciprofloxacin. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism.

Elimination: The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. The urinary excretion of Ciprofloxacin is virtually complete within 24 hours after dosing.

INDICATIONS AND USAGE

In following indications, Uzaril should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

Adults:

Uncomplicated cystitis

- --Uncomplicated acute cystitis
- --Simple uncomplicated acute cystitis
- --Acute cystitis in women
- --Simple uncomplicated acute cystitis in the premenopausal adult women
- --Recurrent cystitis in women
- --Acute uncomplicated infection of lower urinary tract (simple cystitis)
- --Acute pyelonephritis
- --Complicated urinary tract infections
- --Bacterial prostatitis.

Acute exacerbation of chronic bronchitis and of chronic obstructive pulmonary disease

- --Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis
- --Acute exacerbations of chronic bronchitis
- --Exacerbation of chronic obstructive pulmonary disease

Acute bacterial rhinosinusitis

- --Acute sinusitis
- --Acute bacterial sinusitis

Otitis media acute

Gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*

Infections of the bones and joints

Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

DOSAGE AND ADMINISTRATION

Dosage in Adults: The determination of dosage and duration for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative microorganism, the integrity of the patient's host-defense mechanisms and the status of renal and hepatic function.

ADULT DOSAGE GUIDELINES

----Infection	Dose	Frequency	Usual Durations ¹
----Bone and Joint	500-750 mg	every 12 hours	4 to 8 weeks
----Uncomplicated Urethral and	250 mg	single dose	single dose
----Cervical Gonococcal Infections			
----Chronic Bacterial Prostatitis	500 mg	every 12 hours	28 days
----Lower Respiratory Tract Infections	500-750 mg	every 12 hours	7 to 14 days
----Urinary Tract Infections	250-500 mg	every 12 hours	7 to 14 days
----Acute Uncomplicated Cystitis	250 mg	every 12 hours	3 days
----Acute Sinusitis	500 mg	every 12 hours	10 days

Generally Ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared.

Patients with hepatic and renal impairment: In patients with impaired liver function no dose adjustment is required.

In patients with reduced renal function the half-life of Ciprofloxacin is slightly prolonged. Dosage adjustments may be required.

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

----- Creatinine Clearance (mL/min)	Dose
----- > 50	See Usual Dosage.
----- 30-50	250-500 mg every 12 hours
----- 5-29	250-500 mg every 18 hours
----- Patients on hemodialysis or Peritoneal dialysis	250-500 mg every 24 hours (after dialysis)

ADVERSE REACTIONS

Adult Patients: The most frequently reported adverse reactions, from clinical trials of all formulations all dosages, all drug-therapy durations and for all indications of Ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), abnormal liver function tests (1.3%), vomiting (1%) and rash (1%).

- - Musculoskeletal and connective tissue disorders*
- - Nervous system disorders*
- - General disorders and administrative site conditions*
- - Psychiatric disorders*
- - Eye disorders*
- - Ear and labyrinth disorders*

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

DRUG INTERACTIONS

Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Co-administration of Ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the co-administered drug.

Tizanidine: Concomitant administration of tizanidine and Ciprofloxacin is contraindicated due to the potentiation of hypotensive and sedative effects of tizanidine.

Theophylline: Avoid Use (plasma exposure likely to be increased and prolonged) concurrent administration of Ciprofloxacin with theophylline may result in increased risk of a patient developing central nervous system (CNS) or other adverse reactions. If concomitant use cannot be avoided, monitor serum levels of theophylline and adjust dosage as appropriate.

Drugs Known to Prolong QT Interval: Use of Ciprofloxacin may further prolong the QT interval in patients receiving drugs known to prolong the QT interval (for example class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Oral antidiabetic drugs: Fluoroquinolones including Ciprofloxacin have been associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (for example glyburide) or with insulin. In these patients careful monitoring of blood glucose is recommended.

Phenytoin: Simultaneous administration of Ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Anti-coagulant drugs: The risk may vary with the underlying infection, age and general status of the patient so that the contribution of Ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. Monitor prothrombin time and INR frequently during and shortly after co-administration of Ciprofloxacin with an oral anti-coagulant (for example warfarin).

WARNINGS AND PRECAUTIONS

The use of Ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products. Treatment of these patients with Ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Prolonged, disabling and potentially irreversible serious adverse drug reactions: Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture: Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Peripheral neuropathy: Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Ciprofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition.

Central Nervous System Effects: Fluoroquinolones including Ciprofloxacin have been associated with an increased risk of central nervous system (CNS) effects including convulsions, increased intracranial pressure (including pseudotumor cerebri) and toxic psychosis. Ciprofloxacin may also cause central nervous system (CNS) events including: nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression and psychotic reactions have progressed to suicidal ideations/thoughts and self-injurious behavior such as attempted or completed suicide. These reactions may occur following the first dose. Advise patients receiving Ciprofloxacin to inform their healthcare provider immediately if these reactions occur.

Exacerbation of Myasthenia Gravis: Fluoroquinolones including Ciprofloxacin have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and requirement for ventilatory support have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid Ciprofloxacin in patients with known history of myasthenia gravis.

Other Serious and Sometimes Fatal Adverse Reactions: Other serious and sometimes fatal adverse reactions, some due to hypersensitivity and some due to uncertain etiology have been reported in patients receiving therapy with quinolones including Ciprofloxacin.

Fever, rash, or severe dermatologic reactions (for example, toxic epidermal necrolysis, Stevens-Johnson syndrome), vasculitis arthralgia, myalgia, serum sickness, allergic pneumonitis, interstitial nephritis, acute renal insufficiency or failure, hepatitis, jaundice, acute hepatic necrosis or failure, anemia including hemolytic and aplastic thrombocytopenia, thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia and/or other hematologic abnormalities.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother.

Nursing Mothers: Ciprofloxacin is excreted in human milk. The amount of Ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential risk of serious adverse reactions (including articular damage) in infants nursing from mothers taking Ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Although effective in clinical trials Ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to controls. Quinolones including Ciprofloxacin cause arthropathy in juvenile animals.

Geriatric Use: Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as Ciprofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy.

Renal Impairment: Ciprofloxacin is eliminated primarily by renal excretion however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine.

Hepatic Impairment: In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in Ciprofloxacin pharmacokinetics have been observed. The pharmacokinetics of Ciprofloxacin in patients with acute hepatic insufficiency have not been studied.

OVERDOSAGE

In the event of acute overdosage reversible renal toxicity has been reported in some cases. Empty the stomach by inducing vomiting or by gastric lavage. Observe the patient carefully and give supportive treatment including monitoring of renal function, urinary pH and acidify, if required to prevent crystalluria and administration of magnesium, aluminum or calcium containing antacids which can reduce the absorption of Ciprofloxacin. Adequate hydration must be maintained. Only a small amount of Ciprofloxacin (less than 10%) is removed from the body after hemodialysis or peritoneal dialysis.

CONTRAINDICATIONS

Hypersensitivity: Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to Ciprofloxacin any member of the quinolone class of antibacterials or any of the product components. Concomitant administration with tizanidine is contraindicated.

PRESENTATION

Uzaril 250mg Tablet : 1x10's/pack
Uzaril 500mg Tablet : 1x10's/pack

DOSAGE:

As directed by the physician.

INSTRUCTIONS:

Store below 30°C.

Protect from sunlight and moisture.

Keep out of reach of children.

Detailed prescribing information is available on request.

 Manufactured by:
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An ISO Certified Company

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