CIPRO® XR

(ciprofloxacin* extended-release tablets)

01/13

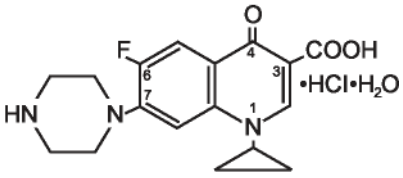
WARNING:
Fluoroquinolones, including CIPRO® XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see WARNINGS).

Fluoroquinolones, including CIPRO XR, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid CIPRO XR in patients with known history of myasthenia gravis (see WARNINGS).

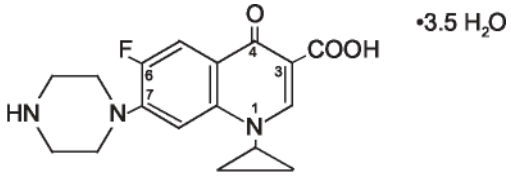
To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO XR and other antibacterial drugs, CIPRO XR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

CIPRO XR (ciprofloxacin* extended-release tablets) contains ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO XR tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7- (1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride. It is provided as a mixture of the monohydrate and the sesquihydrate. The empirical formula of the monohydrate is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its molecular weight is 385.8. The empirical formula of the sesquihydrate is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot 1.5\ H_2O$ and its molecular weight is 394.8. The drug substance is a faintly yellowish to light yellow crystalline substance. The chemical structure of the monohydrate is as follows:



Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. As a hydrate, its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot 3.5\ H_2O$ and its molecular weight is 394.3. It is a pale yellowish to light yellow crystalline substance and its chemical structure is as follows:



CIPRO XR is available in 500 mg and 1000 mg (ciprofloxacin equivalent) tablet strengths. CIPRO XR tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. Each CIPRO XR 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin HCl (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin† (212.6 mg, calculated on the dried basis). Each CIPRO XR 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin HCl (574.9 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin† (425.2 mg, calculated on the dried basis). The inactive ingredients are crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.

* as ciprofloxacin† and ciprofloxacin hydrochloride

† does not comply with the loss on drying test and residue on ignition test of the USP monograph.

CLINICAL PHARMACOLOGY

Absorption

CIPRO XR tablets are formulated to release drug at a slower rate compared to immediate-release tablets. Approximately 35% of the dose is contained within an immediate-release component, while the remaining 65% is contained in a slow-release matrix.

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with CIPRO XR. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-release BID treatment, the C_{max} of CIPRO XR 500 mg and 1000 mg once daily are higher than the corresponding BID doses, while the AUCs over 24 hours are equivalent.

The following table compares the pharmacokinetic parameters obtained at steady state for these four treatment regimens (500 mg QD CIPRO XR versus 250 mg BID ciprofloxacin immediate-release tablets and 1000 mg QD CIPRO XR versus 500 mg BID ciprofloxacin immediate-release).

Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO® and CIPRO XR Administration

	C_{max} (mg/L)	$AUC_{0\text{-}24h}$ (mg•h/L)	$T_{1/2}$ (hr)	T_{max} (hr) §
CIPRO XR 500 mg QD	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1 – 2.5)
CIPRO 250 mg BID	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1 (0.5 – 2.5)
CIPRO XR 1000 mg QD	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2 (1 – 4)
CIPRO 500 mg BID	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2 (0.5 – 3.5)

§ median (range)

Results of the pharmacokinetic studies demonstrate that CIPRO XR may be administered with or without food (for example, high-fat and low-fat meals or under fasted conditions).

Distribution

The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 – 2.7 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. 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. Following administration of a single dose of CIPRO XR, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500 mg and 1000 mg tablets; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58 mg/L for the 1000 mg tablet.

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration 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 coadministered drug (see **CONTRAINDICATIONS; WARNINGS; PRECAUTIONS: Drug Interactions**).

Elimination

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the CIPRO XR tablet. In studies comparing the CIPRO XR and immediate-release ciprofloxacin, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Special Populations

Pharmacokinetic studies of the immediate-release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See **PRECAUTIONS, Geriatric Use**.)

Patients with Renal Impairment

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO XR should be reduced to CIPRO XR 500 mg q24h in patients with creatinine clearance equal to or below 30 mL/min. (See **DOSAGE AND ADMINISTRATION**.)

Patients with Hepatic Impairment

In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See **DOSAGE AND ADMINISTRATION**.)

Drug-Drug Interactions

Concomitant administration with tizanidine is contraindicated. (See **CONTRAINDICATIONS**). Previous studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc. (See **WARNINGS: PRECAUTIONS**, **Drug Interactions** and **Information for Patients**, and **DOSAGE AND ADMINISTRATION**.)

Antacids

When CIPRO XR given as a single 1000 mg dose was administered two hours before, or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible. (See **PRECAUTIONS, Information for Patients and Drug Interactions,** and **DOSAGE AND ADMINISTRATION**.)

Omeprazole

When CIPRO XR was administered as a single 1000 mg dose concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined. (See **PRECAUTIONS, Drug Interactions**.)

MICROBIOLOGY

Mechanism of Action

The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination.

Mechanism of Resistance

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides;therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. Resistance to fluoroquinolones occurs primarily by either mutations in the DNA gyrases, decreased outer membrane permeability, or drug efflux. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations. Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $< 10^{-9}$ to $1x10^{-6}$.

Cross Resistance

There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials.

Ciprofloxacin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO XR (ciprofloxacin extended release tablets).

Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates only)

Staphylococcus saprophyticus

Gram-negative bacteria

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

The following *in vitro* data are available, **but their clinical significance is unknown.** At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ciprofloxacin (≤1 mcg/mL). However, the efficacy of ciprofloxacin in treating clinical infections due to these bacteria **has not been** established in adequate and well-controlled clinical trials.

Gram-negative bacteria

Citrobacter koseri (*diversus*)	*Morganella morganii*
Citrobacter freundii	*Proteus vulgaris*
Edwardsiella tarda	*Providencia rettgeri*
Enterobacter aerogenes	*Providencia stuartii*
Enterobacter cloacae	*Serratia marcescens*
Klebsiella oxytoca	

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

- **Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar).[1,3] The MIC values should be interpreted according to criteria provided in Table 1 .
- **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.[2,3] This procedure uses paper disks impregnated with 5 mcg ciprofloxacin to test the susceptibility of bacteria to ciprofloxacin. The disc diffusion interpretive criteria are provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Ciprofloxacin						
	MIC (mcg/mL)			Zone Diameter (mm)		
Bacteria	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤1	2	≥4	≥21	16–20	≤15
Enterococcus faecalis	≤1	2	≥4	≥21	16–20	≤15
Pseudomonas aeruginosa	≤1	2	≥4	≥21	16–20	≤15
Staphylococcus saprophyticus	≤1	2	≥4	≥21	16–20	≤15
S=Susceptible, I=Intermediate, and R=Resistant.						

A report of "Susceptible" indicates that antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the site of infection necessary to inhibit growth of the pathogen. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

- **Quality Control:** Standardized susceptibility test procedures require the use of laboratory controls to monitor the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test [1,2] Standard ciprofloxacin powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the ciprofloxacin 5 mcg disk the criteria in Table 2 should be achieved ..

Table 2: Acceptable Quality Control Ranges for Ciprofloxacin		
Bacteria	**MIC range (mcg/mL)**	**Zone Diameter (mm)**
Enterococcus faecalis ATCC 29212	0.25–2	-
Escherichia coli ATCC 25922	0.004–0.015	30–40
Pseudomonas aeruginosa ATCC 27853	0.25–1.0	25–33
Staphylococcus aureus ATCC29213	0.12–0.5	-
Staphylococcus aureus ATCC25923	-	22–30

INDICATIONS AND USAGE

CIPRO XR is indicated only for the treatment of urinary tract infections, including acute uncomplicated pyelonephritis, caused by susceptible isolates of the designated microorganisms as listed below. CIPRO

XR and ciprofloxacin immediate-release tablets are not interchangeable. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli, Proteus mirabilis,* vancomycin-susceptible *Enterococcus faecalis, or Staphylococcus saprophyticus.*

Complicated Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae,* vancomycin-susceptible *Enterococcus faecalis, Proteus mirabilis, or Pseudomonas aeruginosa**.

Acute Uncomplicated Pyelonephritis caused by *Escherichia coli.*

*Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

THE SAFETY AND EFFICACY OF CIPRO XR IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED. Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO XR may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO XR and other antibacterial drugs, CIPRO XR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.

Concomitant administration with tizanidine is contraindicated. (See **PRECAUTIONS: Drug Interactions**.)

WARNINGS

Tendinopathy and Tendon Rupture

Fluoroquinolones, including CIPRO XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Inflammation and tendon rupture can occur, sometimes bilaterally, even within the first 48 hours, during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO XR should be used with caution in patients with a history of tendon disorders. CIPRO XR should be discontinued if

the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including CIPRO XR, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid CIPRO XR in patients with known history of myasthenia gravis. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS: Post-Marketing Adverse Event Reports**).

Pregnant Women

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS:, Pregnancy, and Nursing Mothers subsections**.)

Hypersensitivity Reactions:

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous fluids, intravenous steroids, and airway management, should be administered as indicated.

Other Serious and Sometimes Fatal Reactions

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- 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, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (see **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**).

Hepatobiliary System

Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, and fatal events, have been reported with ciprofloxacin. Acute liver injury is rapid in onset (range 1-39 days), and is often associated with hypersensitivity. The pattern of injury can be hepatocellular, cholestatic or

mixed. Most patients with fatal outcomes were older than 55 years old. In the event of any signs and symptoms of hepatitis (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued immediately (see **ADVERSE REACTIONS**).

There can be a temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin (see **ADVERSE REACTIONS**).

Theophylline

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF INTRAVENOUS CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse events have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Central Nervous System Effects

Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis have been reported in patients receiving fluoroquinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, 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. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued, patients should be advised to inform their healthcare provider immediately and appropriate measures instituted. As with all fluoroquinolones, ciprofloxacin should be used with caution in epileptic patients and patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, previous history of convulsion, reduced cerebral blood flow, altered brain structure, or stroke), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). CIPRO XR should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible undesirable CNS side effects. Cases of status epilepticus have been reported. If seizures occur, ciprofloxacin should be discontinued. (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS**.**)**

***Clostridium Difficile* Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CIPRO, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Peripheral Neuropathy

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition. Patients treated with CIPRO XR should be advised to inform their healthcare provider prior to continuing treatment if symptoms of neuropathy develop.

Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in the **INDICATIONS AND USAGE** section. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS**.)

The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Prolongation of the QT Interval

Some fluoroquinolones, including ciprofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during postmarketing surveillance in patients receiving fluoroquinolones, including ciprofloxacin. ciprofloxacin should be avoided in patients with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes (for example, congenital long QT syndrome , uncorrected electrolyte imbalance, such as hypokalemia or hypomagnesemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA antiarrhythmic agents (quinidine, procainamide), or Class III antiarrhythmic agents (amiodarone, sotalol) , tricyclic antidepressants, macrolides, and antipsychotics. Elderly patients may also be more susceptible to drug-associated effects on the QT interval. (See **PRECAUTIONS, Drug Interactions and Geriatric Use.**)

Cytochrome P450 (CYP450)

Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (for example, theophylline, methylxanthines, caffeine, tizanidine, ropinirole, clozapine, olanzapine)) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug. (See **PRECAUTIONS, Drug Interactions**.)

PRECAUTIONS

General

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See **ANIMAL PHARMACOLOGY**.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS, Information for Patients,** and **Drug Interactions**.)

Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (for example, burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs (see **ADVERSE REACTIONS).**

Prescribing CIPRO XR in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients:

Patients should be advised:

- To contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO XR treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- That fluoroquinolones like CIPRO XR may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.
- That antibacterial drugs including CIPRO XR should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO XR is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CIPRO XR or other antibacterial drugs in the future.
- That CIPRO XR may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration with magnesium/aluminum antacids, polymeric phosphate binders (for example, sevelamer, lanthanum carbonate) or sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or with other products containing calcium, iron, or zinc should be avoided. CIPRO XR may be taken two hours before or six hours after taking these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions**.) CIPRO XR should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, CIPRO XR may be taken with a meal that contains these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions**.)

- If the patient should forget to take CIPRO XR at the usual time, he/she may take the dose later in the day. Do not take more than one CIPRO XR tablet per day even if a patient misses a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**
- That ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue CIPRO XR at the first sign of a skin rash or other allergic reaction.
- That photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.
- That peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.
- That CIPRO XR may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- That ciprofloxacin increases the effects of tizanidine (Zanaflex®). Patients should not use ciprofloxacin if they are already taking tizanidine.
- That CIPRO XR may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.
- That convulsions have been reported in patients receiving quinolones, including ciprofloxacin, and to notify their physician before taking CIPRO XR if there is a history of this condition.
- That diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

Tizanidine

In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (C_{max} 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg bid for 3 days). The hypotensive and sedative effects of tizanidine were also potentiated. Concomitant administration of tizanidine and ciprofloxacin is contraindicated. (See **CONTRAINDICATIONS**.)

Theophylline

As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See **WARNINGS**.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Other Xanthine Derivatives

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life. On concurrent

administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products, elevated serum concentrations of these xanthine derivatives were reported.

Chelation Complex Formation

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Information for Patients,** and **DOSAGE AND ADMINISTRATION**.)

Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Omeprazole

Concomitant administration of a single tablet dose of 500 mg ciprofloxacin and once-daily administration of 20 mg omeprazole pretreatment for 4 days resulted in a 16% reduction of mean C_{max} and mean AUC of ciprofloxacin (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions**.)

Phenytoin

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related undesirable effects when ciprofloxacin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of CIPRO XR with phenytoin.

Oral Antidiabetic Agents

Hypoglycemia has been reported when ciprofloxacin and oral antidiabetic agents, mainly sulfonylureas (for example, glyburide, glimepiride), were co-administered, presumably by intensifying the action of the oral antidiabetic agent (see **ADVERSE REACTIONS**). The concomitant administration of ciprofloxacin with glyburide has, on rare occasions, resulted in severe hypoglycemia.

Metronidazole

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Cyclosporine

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Oral Anticoagulants

Simultaneous administration of ciprofloxacin with an oral anticoagulantmay augment the effect of the anticoagulant. 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. Prothrombin time and INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant (for example, warfarin).

Probenecid

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Metoclopramide

Metoclopramide significantly accelerates the absorption of oral ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

Duloxetine

In clinical studies it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in a 5-fold increase of mean AUC and a 2.5-fold increase in mean C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

NSAIDs

Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

Ropinirole

In a study conducted in 12 patients with Parkinson's disease who were administered 6 mg ropinirole once daily with 500 mg ciprofloxacin twice-daily, the mean C_{max} and mean AUC of ropinirole were increased by 60% and 84%, respectively. Monitoring for ropinirole-related side effects and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with ciprofloxacin. (See **Warnings, Cytochrome P450**.)

Lidocaine

In a study conducted in 9 healthy volunteers, concomitant use of 1.5 mg/kg IV lidocaine with 500 mg ciprofloxacin twice daily, resulted in an increase of lidocaine C_{max} and AUC by 12% and 26%, respectively. Although lidocaine treatment was well tolerated at this elevated exposure, a possible interaction with ciprofloxacin and an increase in side effects related to lidocaine may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with 304 mg clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Careful monitoring of clozapine associated adverse effects and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised. (See **WARNINGS.**)

Sildenafil

Following concomitant administration of a single oral dose of 50 mg sildenafil with 500 mg ciprofloxacin to healthy subjects, the mean C_{max} and mean AUC of sildenafil were both increased approximately two-fold. Therefore, sildenafil should be used with caution when co-administered with ciprofloxacin.

Drugs known to prolong QT interval

Precaution should be taken when using ciprofloxacin concomitantly with drugs known to prolong the QT interval (for example, class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) as ciprofloxacin may have an additive effect on the QT interval (see **Warnings and Precautions**, **Geriatric Use**).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)

E. coli DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V_{79} Cell HGPRT Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae Point Mutation Assay (Negative)

Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)

Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay

Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Ciprofloxacin was not carcinogenic or tumorigenic in 2-year carcinogenicity studies with rats and mice at daily oral dose levels of 250 and 750 mg/kg, respectively (approximately 2 and 3 -fold greater than the 1000 mg daily human dose based upon body surface area).

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to the maximum recommended daily human dose of 1000 mg based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (1 times the highest recommended daily human dose of 1000 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy

Teratogenic Effects. Pregnancy Category C

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

WARNINGS). An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS - the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state there is no risk.

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation. In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy. However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for the less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.7 and 0.4 times the maximum daily human dose of 1000 mg based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

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

Safety and effectiveness of CIPRO XR in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO XR. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRO XR to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue CIPRO XR and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning, WARNINGS,** and **ADVERSE REACTIONS)**.

In a large, prospective, randomized CIPRO XR clinical trial in complicated urinary tract infections, 49% (509/1035) of the patients were 65 and over, while 30% (308/1035) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and clinical experience with other formulations of ciprofloxacin has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using CIPRO XR with concomitant drugs that can result in prolongation of the QT interval (for example, class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (for example, known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS

Clinical trials in patients with urinary tract infections enrolled 961 patients treated with 500 mg or 1000 mg CIPRO XR. Most adverse events reported were described as mild to moderate in severity and required no treatment. The overall incidence, type and distribution of adverse events were similar in patients receiving both 500 mg and 1000 mg of CIPRO XR. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates observed in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In the clinical trial of uncomplicated urinary tract infection, CIPRO XR (500 mg once daily) in 444 patients was compared to ciprofloxacin immediate-release tablets (250 mg twice daily) in 447 patients for 3 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 0.2% (1/444) of patients in the CIPRO XR arm and in 0% (0/447) of patients in the control arm.

In the clinical trial of complicated urinary tract infection and acute uncomplicated pyelonephritis, CIPRO XR (1000 mg once daily) in 517 patients was compared to ciprofloxacin immediate-release tablets (500 mg twice daily) in 518 patients for 7 to 14 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 3.1% (16/517) of patients in the CIPRO XR arm and in 2.3% (12/518) of patients in the control arm. The most common reasons for discontinuation in the CIPRO XR arm were nausea/vomiting (4 patients) and dizziness (3 patients). In the control arm the most common reason for discontinuation was nausea/vomiting (3 patients).

In these clinical trials, the following events occurred in ≥ 2% of all CIPRO XR patients, regardless of drug relationship: nausea (4%), headache (3%), dizziness (2%), diarrhea (2%), vomiting (2%) and vaginal moniliasis (2%).

Adverse events, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of all CIPRO XR treated patients were: nausea (3%), diarrhea (2%), headache (1%), dyspepsia (1%), dizziness (1%), and vaginal moniliasis (1%). Vomiting (1%) occurred in the 1000 mg group.

Additional uncommon events, judged by investigators to be at least possibly drug-related, that occurred in less than 1% of CIPRO XR treated patients were:

BODY AS A WHOLE: abdominal pain, asthenia, malaise, photosensitivity reaction

CARDIOVASCULAR: bradycardia, migraine, syncope

DIGESTIVE: anorexia, constipation, dry mouth, flatulence, liver function tests abnormal, thirst

HEMIC/LYMPHATIC: prothrombin decrease

CENTRAL NERVOUS SYSTEM: convulsive seizures (including status epilepticus) abnormal dreams, depersonalization, depression (potentially culminating in self-injurious behavior, such as suicidal ideations/thoughts and attempted or completed suicide), hypertonia, incoordination, insomnia, somnolence, tremor, vertigo

METABOLIC: hyperglycemia, hypoglycemia

SKIN/HYPERSENSIVITY: dry skin, maculopapular rash, photosensitivity/phototoxicity reactions, pruritus, rash, skin disorder, urticaria, vesiculobullous rash

SPECIAL SENSES: diplopia, taste perversion

UROGENITAL: dysmenorrhea, hematuria, kidney function abnormal, vaginitis

Post-Marketing Adverse Event Reports: The following adverse events have been reported from worldwide marketing experience with fluoroquinolones, including ciprofloxacin. Because these reactions have been reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or a causal relationship to drug exposure.

The events in alphabetical order are:

abnormal gait, achiness, acidosis, acute generalized exanthematous pustulosis (AGEP), agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions and including life-threatening anaphylactic shock), amylase increase, anemia, angina pectoris, angioedema, anosmia, anxiety, arrhythmia, arthralgia, ataxia, atrial flutter, bleeding diathesis, blurred vision, bronchospasm, *C. difficile* associated diarrhea, candidiasis (cutaneous, oral), candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, cholestatic jaundice, chromatopsia, confusion, convulsion, delirium, drowsiness, dysphagia, dysphasia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, fixed eruptions, flushing, gastrointestinal bleeding, gout (flare up), grand mal convulsion, gynecomastia, hallucinations, hearing loss, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic failure (including fatal cases), hepatic necrosis, hepatitis, hiccup, hyperesthesia, hyperpigmentation, hypertension, hypertonia, hypesthesia, hypotension, ileus, International Normalized Ratio (INR) increased (in patients treated with Vitamin K antagonists), interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lipase increase, lymphadenopathy, manic reaction, marrow depression, migraine, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, exacerbation of myasthenia gravis, myocardial infarction, myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest, epigastric, eye, extremities, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, pancytopenia, paranoia, paresthesia, peripheral neuropathy, perspiration (increased), petechia, phlebitis, phobia, photosensitivity/phototoxicity reaction, pleural effusion, polyuria, postural hypotension, prothrombin time prolongation, pseudomembranous colitis (the onset of symptoms may occur during or after antimicrobial treatment), pulmonary embolism, purpura, renal calculi, renal failure, respiratory arrest, respiratory distress, restlessness, serum sickness-like reaction, Stevens-Johnson syndrome, sweating, tachycardia, taste loss, tendinitis, tendon rupture, tinnitus, torsade de pointes, toxic epidermal necrolysis (Lyell's syndrome), toxic psychosis, QT prolongation, twitching, unresponsiveness, urethral bleeding, urinary retention, urination (frequent), vaginal pruritus, vasculitis, ventricular ectopy, vesicles, visual acuity (decreased), visual disturbances (flashing lights, change in color perception, overbrightness of lights).

Laboratory Changes:

The following adverse laboratory changes, in alphabetical order, regardless of incidence or relationship to drug, have been reported in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications):

Decreases in blood glucose, BUN, hematocrit, hemoglobin, leukocyte counts, platelet counts, prothrombin time, serum albumin, serum potassium, total serum protein, uric acid.

Increases in alkaline phosphatase, ALT (SGPT), AST (SGOT), atypical lymphocyte counts, blood glucose, blood monocytes, BUN, cholesterol, eosinophil counts, LDH, platelet counts, prothrombin time, sedimentation rate, serum amylase, serum bilirubin, serum calcium, serum cholesterol, serum creatine phosphokinase, serum creatinine, serum gamma-glutamyl transpeptidase (GGT), serum potassium, serum theophylline (in patients receiving theophylline concomitantly), serum triglycerides, uric acid.

Others: albuminuria, change in serum phenytoin, crystalluria, cylindruria, immature WBCs, leukocytosis, methemoglobinemia, pancytopenia.

OVERDOSAGE

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

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin > 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

DOSAGE AND ADMINISTRATION

CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable. Cipro XR should be administered orally once daily as described in the following Dosage Guidelines table:

DOSAGE GUIDELINES

Indication	Unit Dose	Frequency	Usual Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis)	500 mg	Q24h	3 Days
Complicated Urinary Tract Infection	1000 mg	Q24h	7-14 Days

Acute Uncomplicated Pyelonephritis	1000 mg	Q24h	7-14 Days

Patients whose therapy is started with CIPRO I.V. for urinary tract infections may be switched to CIPRO XR when clinically indicated at the discretion of the physician.

CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, polymeric phosphate binders (for example, sevelamer, lanthanum carbonate), as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible. A 2-hour window between substantial calcium intake (> 800 mg) and dosing with CIPRO XR is recommended. CIPRO XR should be swallowed whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.** (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Drug Interactions** and **Information for Patients**.**)**

Impaired Renal Function:

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. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. No dosage adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. In patients with complicated urinary tract infections and acute uncomplicated pyelonephritis, who have a creatinine clearance of ≤ 30 mL/min, the dose of CIPRO XR should be reduced from 1000 mg to 500 mg daily. The use of Ciprofloxacin 1000 mg XR tablets is not recommended in this patient population.

For patients on hemodialysis or peritoneal dialysis, administer CIPRO XR after the dialysis procedure is completed (maximum dose should be Ciprofloxacin 500 mg XR q 24 h). The use of Ciprofloxacin 1000 mg XR is not recommended in this patient population. (See **CLINICAL PHARMACOLOGY, Special Populations,** and **PRECAUTIONS, Geriatric Use**.)

For patients on continuous ambulatory peritoneal dialysis (CAPD), the maximum dose should be 500 mg q 24h.

Impaired Hepatic Function:

No dosage adjustment is required with CIPRO XR in patients with stable chronic cirrhosis. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See **CLINICAL PHARMACOLOGY, Special Populations**.)

Children and Adolescents

Dosing in children (less than 18 years of age) with impaired renal or hepatic function has not been studied.

HOW SUPPLIED

CIPRO XR is available as nearly white to slightly yellowish, film-coated, oblong-shaped tablets containing 500 mg or 1000 mg ciprofloxacin. The 500 mg tablet is coded with the word “BAYER” on one side and “C500 QD” on the reverse side. The 1000 mg tablet is coded with the word “BAYER” on one side and “C1000 QD” on the reverse side.

	Strength	NDC Code
Bottles of 50	500 mg	50419-788-01
Bottles of 50	1000 mg	50419-789-01

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg no effects on joints were observed. This dose was also not associated with arthrotoxicity after an additional treatment-free period of 5 months. In another study, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral doses as low as 5 mg/kg (approximately 0.1-times the highest recommended therapeutic dose based upon mg/m^2. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration (approximately 0.4 times the highest recommended therapeutic dose based upon mg/m^2).

In dogs. ciprof1oxacin adinistered at 3 and 10 mg/kg by rapid infusion injection (15 sec.) produces hypotensive effects. These effects are considered to be related to histamine release because they are partially antagonized by pyrilamine. an antihistamine. In rhesus monkeys, rapid infusion injection also produces hypotension. but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

CLINICAL STUDIES

Uncomplicated Urinary Tract Infections (acute cystitis)

CIPRO XR was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in a randomized, double-blind, controlled clinical trial conducted in the US. This study compared CIPRO XR (500 mg once daily for three days) with ciprofloxacin immediate-release tablets (CIPRO® 250 mg BID for three days). Of the 905 patients enrolled, 452 were randomly assigned to the CIPRO XR treatment group and 453 were randomly assigned to the control group. The primary efficacy variable was bacteriologic eradication of the baseline organism(s) with no new infection or superinfection at test-of-cure (Day 4 -11 Post-therapy).

The bacteriologic eradication and clinical success rates were similar between CIPRO XR and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (CIPRO XR minus control group) are given in the following table:

	CIPRO XR 500 mg QD x 3 Days	CIPRO 250 mg BID x 3 Days
Randomized Patients	452	453
Per Protocol Patients†	199	223
Bacteriologic Eradication at TOC (n/N)*	188/199 (94.5%)	209/223 (93.7%)
	CI [-3.5%, 5.1%]	
Bacteriologic Eradication (by organism) at TOC (n/N)**		
E. coli	156/160 (97.5%)	176/181 (97.2%)
E. faecalis	10/11 (90.9%)	17/21 (81%)
P. mirabilis	11/12 (91.7%)	7/7 (100%)
S. saprophyticus	6/7 (85.7%)	9/9 (100%)
Clinical Response at TOC (n/N)***	189/199 (95%)	204/223 (91.5%)
	CI [-1.1%, 8.1%]	

* n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/ total number of patients

** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism

*** n/N = patients with clinical success /total number of patients

† The presence of a pathogen at a level of $\geq 10^5$ CFU/mL was required for microbiological evaluability criteria, except for *S. saprophyticus* ($\geq 10^4$ CFU/mL).

Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

CIPRO XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients (521 patients per treatment arm) and compared CIPRO XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg BID for 7 to 14 days). The primary efficacy endpoint for this trial was bacteriologic eradication of the baseline organism(s) with no new infection or superinfection at 5 to 11 days post-therapy (test-of-cure or TOC) for the Per Protocol and Modified Intent-To-Treat (MITT) populations.

The Per Protocol population was defined as patients with a diagnosis of cUTI or AUP, a causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, no inclusion criteria violation, a valid test-of-cure urine culture within the TOC window, an organism susceptible to study drug, no premature discontinuation or loss to follow-up, and compliance with the dosage regimen (among other criteria). More patients in the CIPRO XR arm than in the control arm were excluded from the Per Protocol population and this should be considered in the interpretation of the study results. Reasons for exclusion with the greatest discrepancy between the two arms were no valid test-of-cure urine culture, an organism resistant to the study drug, and premature discontinuation due to adverse events.

An analysis of all patients with a causative organism(s) isolated at baseline and who received study medication, defined as the MITT population, included 342 patients in the CIPRO XR arm and 324 patients in the control arm. Patients with missing responses were counted as failures in this analysis. In the MITT analysis of cUTI patients, bacteriologic eradication was 160/271 (59%) versus 156/248 (62.9%) in CIPRO XR and control arm, respectively [97.5% CI* (-13.5%, 5.7%)]. Clinical cure was 184/271 (67.9%) for CIPRO XR and 182/248 (73.4%) for control arm, respectively [97.5% CI* (-14.4%, 3.5%)]. Bacterial eradication in the MITT analysis of patients with AUP at TOC was 47/71 (66.2%) and 58/76

(76.3%) for CIPRO XR and control arm, respectively [97.5% CI* (-26.8%, 6.5%)]. Clinical cure at TOC was 50/71 (70.4%) for CIPRO XR and 58/76 (76.3%) for the control arm [97.5% CI* (-22.0%, 10.4%)].

* confidence interval of the difference in rates (CIPRO XR minus control).

In the Per Protocol population, the differences between CIPRO XR and the control arm in bacteriologic eradication rates at the TOC visit were not consistent between AUP and cUTI patients. The bacteriologic eradication rate for cUTI patients was higher in the CIPRO XR arm than in the control arm. For AUP patients, the bacteriologic eradication rate was lower in the CIPRO XR arm than in the control arm. This inconsistency was not observed between the two treatment groups for clinical cure rates. Clinical cure rates were 96.1% (198/206) and 92.1% (211/229) for CIPRO XR and the control arm, respectively.

The bacterial eradication and clinical cure rates by infection type for CIPRO XR and the control arm at the TOC visit and their corresponding 97.5% confidence intervals for the differences between rates (CIPRO XR minus control arm) are given below for the Per Protocol population analysis:

	CIPRO XR 1000 mg QD	**CIPRO 500 mg BID**
Randomized Patients	521	521
Per Protocol Patients^	206	229
cUTI Patients		
Bacteriologic Eradication at TOC (n/N)*	148/166 (89.2%)	144/177 (81.4%)
	CI [-0.7%, 16.3%]	
Bacteriologic Eradication (by organism) at TOC (n/N)**		
E. coli	91/94 (96.8%)	90/92 (97.8%)
K. pneumoniae	20/21 (95.2%)	19/23 (82.6%)
E. faecalis	17/17 (100%)	14/21 (66.7%)
P. mirabilis	11/12 (91.6%)	10/10 (100%)
P. aeruginosa	3/3 (100%)	3/3 (100%)
Clinical Cure at TOC (n/N)***	159/166 (95.8%)	161/177 (91.0%)
	CI [-1.1%, 10.8%]	
AUP Patients		
Bacteriologic Eradication at TOC (n/N)*	35/40 (87.5%)	51/52 (98.1%)
	CI [-34.8%, 6.2%]	
Bacteriologic Eradication of *E. coli* at TOC (n/N)**	35/36 (97.2%)	41/41 (100%)
Clinical Cure at TOC (n/N)***	39/40 (97.5%)	50/52 (96.2%)
	CI [-15.3%, 21.1%]	

^ Patients excluded from the Per Protocol population were primarily those with no causative organism(s) at baseline or no organism present at $\geq 10^5$ CFU/mL at baseline, inclusion criteria violation, no valid test-of-cure urine culture within the TOC window, an organism resistant to study drug, premature discontinuation due to an adverse event, lost to follow-up, or non-compliance with dosage regimen (among other criteria).

* n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/total number of patients

** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism
***n/N = patients with clinical success /total number of patients

Of the 166 cUTI patients treated with CIPRO XR, 148 (89%) had the causative organism(s) eradicated, 8 (5%) had persistence, 5 (3%) patients developed superinfections and 5 (3%) developed new infections. Of the 177 cUTI patients treated in the control arm, 144 (81%) had the causative organism(s) eradicated, 16 (9%) patients had persistence, 3 (2%) developed superinfections and 14 (8%) developed new infections. Of the 40 patients with AUP treated with CIPRO XR, 35 (87.5%) had the causative organism(s) eradicated, 2 (5%) patients had persistence and 3 (7.5%) developed new infections. Of the 5 CIPRO XR AUP patients without eradication at TOC, 4 were considered clinical cures and did not receive alternative antibiotic therapy. Of the 52 patients with AUP treated in the control arm, 51 (98%) had the causative organism(s) eradicated. One patient (2%) had persistence.

REFERENCES

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2.CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 11th Edition. CLSI Document M2-A11, CLSI, Wayne, PA, January, 2012.

3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 22nd Informational Supplement. CLSI Document M100 S22, January 2012.

MEDICATION GUIDE

CIPRO® *(Sip-row)*
(ciprofloxacin hydrochloride)
TABLETS

CIPRO® *(Sip-row)*
(ciprofloxacin)
ORAL SUSPENSION

CIPRO® XR *(Sip-row)*
(ciprofloxacin extended-release tablets)

CIPRO® IV *(Sip-row)*
(ciprofloxacin)
For Intravenous Infusion

Read the Medication Guide that comes with CIPRO® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about CIPRO?

CIPRO belongs to a class of antibiotics called fluoroquinolones. CIPRO can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take CIPRO.

1. Tendon rupture or swelling of the tendon (tendinitis)

- **Tendon problems can happen in people of all ages who take CIPRO.**Tendons are tough cords of tissue that connect muscles to bones. Symptoms of tendon problems may include:
- Pain, swelling, tears and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.
- **The risk of getting tendon problems while you take CIPRO is higher if you:**
  - Are over 60 years of age
  - Are taking steroids (corticosteroids)
  - Have had a kidney, heart or lung transplant
- **Tendon problems can happen in people who do not have the above risk factors when they take CIPRO. Other reasons that can increase your risk of tendon problems can include:**
- Physical activity or exercise
- Kdney failure

- Tendon problems in the past, such as in people with rheumatoid arthritis (RA)

- **Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation.** Stop taking CIPRO until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons.
- **Talk to your healthcare provider about the risk of tendon rupture with continued use of CIPRO.** You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
- **Tendon rupture can happen while you are taking or after you have finished taking CIPRO.** Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
- **Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:**
  - Hear or feel a snap or pop in a tendon area
  - Bruising right after an injury in a tendon area
  - Unable to move the affected area or bear weight

2. Worsening of myasthenia gravis (a disease which causes muscle weakness). Fluoroquinolones like CIPRO may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section "What are the possible side effects of CIPRO?" for more information about side effects.

What is CIPRO?

CIPRO is a fluoroquinolone antibiotic medicine used to treat certain infections caused by certain germs called bacteria.

Children less than 18 years of age have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking CIPRO. CIPRO should not be used as the first choice of antibiotic medicine in children under 18 years of age.

CIPRO Tablets, CIPRO Oral Suspension and CIPRO IV should not be used in children under 18 years old, except to treat specific serious infections, such as complicated urinary tract infections and to prevent anthrax disease after breathing the anthrax bacteria germ (inhalational exposure). It is not known if CIPRO XR is safe and works in children under 18 years of age.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including CIPRO, do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking CIPRO.

Who should not take CIPRO?

Do not take CIPRO if you:

- Have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in CIPRO. Ask your healthcare provider if you are not sure. See the list of ingredients in CIPRO at the end of this Medication Guide.
- Also take a medicine called tizanidine (Zanaflex®). Serious side effects from tizanidine are likely to happen.

What should I tell my healthcare provider before taking CIPRO?

See "**What is the most important information I should know about CIPRO?**".

Tell your healthcare provider about all your medical conditions, including if you:

- Have tendon problems.
- Have a disease that causes muscle weakness (myasthenia gravis).
- Have central nervous system problems (such as epilepsy).
- Have nerve problems.
- Have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation".
- Have a history of seizures.
- Have kidney problems. You may need a lower dose of CIPRO if your kidneys do not work well.
- Have rheumatoid arthritis (RA) or other history of joint problems.
- Have trouble swallowing pills.
- Are pregnant or planning to become pregnant. It is not known if CIPRO will harm your unborn child.
- Are breast-feeding or planning to breast-feed. CIPRO passes into breast milk. You and your healthcare provider should decide whether you will take CIPRO or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal and dietary supplements. CIPRO and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- An NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take CIPRO or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See "**What are the possible side effects of CIPRO?.**"
- A blood thinner (such as warfarin, Coumadin®, Jantoven®).
- Tizanidine (Zanaflex®). You should not take CIPRO if you are already taking tizanidine. See "**Who should not take CIPRO?**".
- Theophylline (such as Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®).
- Glyburide (Micronase®, Glynase®, Diabeta®, Glucovance®). See "What are the possible side effects of CIPRO?".
- Phenytoin (Fosphenytoin Sodium®, Cerebyx®, Dilantin-125®, Dilantin®, Extended Phenytoin Sodium®, Prompt Penytoin Sodium®, Phenytek®).
- Products that contain caffeine.
- A medicine to control your heart rate or rhythm (antiarrhythmics) See "**What are the possible side effects of CIPRO?**".
- An anti-psychotic medicine.
- A tricyclic antidepressant.
- A water pill (diuretic).
- A steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See "**What is the most important information I should know about CIPRO?**".
- Methotrexate (Trexall®)
- Probenecid (Probalan®, Col-probenecid®).
- Metoclopromide (Reglan®, Reglan ODT®).
- Ropinirole (Requip®).
- Lidocaine (Xylocaine® intravenous infusion).
- Clozapine (Clozaril®, Fazaclo® ODT®).
- Pentoxifylline (Trental®).
- Sildenafil (Viagra®, Revatio®).
- Cyclosporine (Gengraf®, Neoral®, Sandimmune®, Sangcya®).
- Omeprazole.
- Certain medicines may keep CIPRO Tablets, CIPRO Oral Suspension from working correctly. Take CIPRO Tablets and Oral Suspension either 2 hours before or 6 hours after taking these products:

- An antacid, multivitamin, or other product that has magnesium, calcium, aluminum, iron, or zinc.
- Sucralfate (Carafate®).
- Didanosine (Videx®, Videx EC®).

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take CIPRO?

- Take CIPRO exactly as prescribed by your healthcare provider.
- Take CIPRO Tablets in the morning and evening at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you can not swallow the tablet whole.
- Take CIPRO Oral Suspension in the morning and evening at about the same time each day. Shake the CIPRO Oral Suspension bottle well each time before use for about 15 seconds to make sure the suspension is mixed well. Close the bottle completely after use.
- Take CIPRO XR one time each day at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you cannot swallow the tablet whole.
- CIPRO IV is given to you by intravenous (IV) infusion into your vein, slowly, over 60 minutes, as prescribed by your healthcare provider.
- CIPRO can be taken with or without food.
- CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone, but may be taken with a meal that contains these products.
- Drink plenty of fluids while taking CIPRO.
- Do not skip any doses, or stop taking CIPRO even if you begin to feel better, until you finish your prescribed treatment, unless:
- You have tendon effects (see “**What is the most important information I should know about CIPRO?”**),
- You have a serious allergic reaction (see “**What are the possible side effects of CIPRO?**”), or
- Your healthcare provider tells you to stop.

This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to CIPRO. If this happens, CIPRO and other antibiotic medicines may not work in the future.

- If you miss a dose of CIPRO Tablets or Oral Suspension, take it as soon as you remember. Do not take two doses at the same time, and do not take more than two doses in one day.
- If you miss a dose of CIPRO XR, take it as soon as you remember. Do not take more than one dose in one day.
- If you take too much, call your healthcare provider or get medical help immediately.

If you have been prescribed CIPRO Tablets, CIPRO Oral Suspension or CIPRO IV after being exposed to anthrax:

CIPRO Tablets, Oral Suspension and IV has been approved to lessen the chance of getting anthrax disease or worsening of the disease after you are exposed to the anthrax bacteria germ.

Take CIPRO exactly as prescribed by your healthcare provider. Do not stop taking CIPRO without talking with your healthcare provider. If you stop taking CIPRO too soon, it may not keep you from getting the anthrax disease.

Side effects may happen while you are taking CIPRO Tablets, Oral Suspension or IV When taking your CIPRO to prevent anthrax infection, you and your healthcare provider should talk about whether the risks of stopping CIPRO too soon are more important than the risks of side effects with CIPRO.

- If you are pregnant, or plan to become pregnant while taking CIPRO, you and your healthcare provider should decide whether the benefits of taking CIPRO Tablets, Oral Suspension or IV for anthrax are more important than the risks.

What should I avoid while taking CIPRO?

- CIPRO can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how CIPRO affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. CIPRO can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking CIPRO, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of CIPRO?

- CIPRO can cause side effects that may be serious or even cause death. See "**What is the most important information I should know about CIPRO?**"

Other serious side effects of CIPRO include:

- **Theophylline**

  You may have serious seizure and breathing problems when you take theophylline with CIPRO. These problems may lead to death. Get emergency help right away if you have seizures or trouble breathing.

- **Central Nervous System effects**

  Seizures have been reported in people who take fluoroquinolone antibiotics including CIPRO. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking CIPRO will change your risk of having a seizure.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of CIPRO. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:

  - Feel dizzy
  - Seizures
  - Hear voices, see things, or sense things that are not there (hallucinations)
  - Feel restless
  - Tremors
  - Feel anxious or nervous
  - Confusion
  - Depression
  - Trouble sleeping
  - Nightmares
  - Feel more suspicious (paranoia)
  - Suicidal thoughts or acts

- **Serious allergic reactions**

  Allergic reactions, including death, can happen in people taking fluoroquinolones, including CIPRO, even after only one dose. Stop taking CIPRO and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:

  - Hives.
  - Trouble breathing or swallowing.
  - Swelling of the lips, tongue, face.
  - Throat tightness, hoarseness.

- Rapid heartbeat.
- Faint.
- Yellowing of the skin or eyes. Stop taking CIPRO and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to CIPRO (a liver problem).

- **Skin rash**

  Skin rash may happen in people taking CIPRO even after only one dose. Stop taking CIPRO at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to CIPRO.

- **Serious heart rhythm changes** (QT prolongation and torsade de pointes)

  Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. CIPRO may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:

  - Who are elderly
  - With a family history of prolonged QT interval
  - With low blood potassium (hypokalemia)
  - Who take certain medicines to control heart rhythm (antiarrhythmics)

- **Intestine infection** (Pseudomembranous colitis)

  Pseudomembranous colitis can happen with most antibiotics, including CIPRO. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

- **Changes in sensation and possible nerve damage** (Peripheral Neuropathy)

  Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including CIPRO. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

  - Pain
  - Burning
  - Tingling
  - Numbness
  - Weakness

CIPRO may need to be stopped to prevent permanent nerve damage.

- **Low blood sugar** (hypoglycemia)

  People who take CIPRO and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar (hypoglycemia) which can sometimes be severe. Tell your healthcare provider if you get low blood sugar with CIPRO. Your antibiotic medicine may need to be changed.

- **Sensitivity to sunlight** (photosensitivity). See "**What should I avoid while taking CIPRO?**".

- **Joint Problems**

  Increased chance of problems with joints and tissues around joints in children under 18 years old. Tell your child's healthcare provider if your child has any joint problems during or after treatment with CIPRO.

  The most common side effects of CIPRO include:

  - Nausea
  - Diarrhea
  - Changes in liver function tests
  - Vomiting
  - Rash
  - Vaginal yeast infection
  - Pain or discomfort in the abdomen
  - Headache

These are not all the possible side effects of CIPRO. Tell your healthcare provider about any side effect that bothers you, or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CIPRO?

- **CIPRO Tablets**
  - Store CIPRO below 86°F (30°C)
- **CIPRO Oral Suspension**
  - Store CIPRO Oral Suspension below 86°F (30°C) for up to 14 days
  - Do not freeze
  - After treatment has been completed, any unused oral suspension should be safely thrown away

- **CIPRO XR**
  - Store CIPRO XR at 59°F to 86°F (15°C to 30°C)

Keep CIPRO and all medicines out of the reach of children.

General Information about CIPRO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CIPRO for a condition for which it is not prescribed. Do not give CIPRO to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about CIPRO. If you would like more information about CIPRO, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CIPRO that is written for healthcare professionals. For more information call 1-888-84 BAYER (1-888-842-2937).

What are the ingredients in CIPRO?

- **CIPRO Tablets**:
  - **Active ingredient:** ciprofloxacin
  - **Inactive ingredients:** cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, and polyethylene glycol
- **CIPRO Oral Suspension:**
  - **Active ingredient:** ciprofloxacin
  - **Inactive ingredients:** The components of the suspension have the following compositions: Microcapsules–ciprofloxacin, povidone, methacrylic acid copolymer, hypromellose, magnesium stearate, and Polysorbate 20. Diluent–medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.
- **CIPRO XR:**
  - **Active ingredient:** ciprofloxacin
  - **Inactive ingredients:** crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.
- **CIPRO IV:**
  - **Active ingredient:** ciprofloxacin

- **Inactive ingredients:** lactic acid as a solubilizing agent, hydrochloric acid for pH adjustment

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Bayer HealthCare

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470
Made in Germany

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