

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVED LABELING

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CIPRO®

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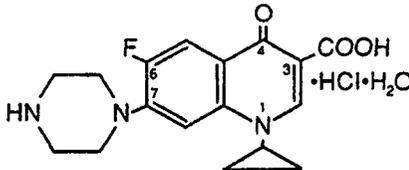
(ciprofloxacin hydrochloride)
TABLETS

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DESCRIPTION

Cipro® (ciprofloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent for oral administration. Ciprofloxacin, a fluoroquinolone, is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows:



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Cipro® is available in 250 mg, 500 mg and 750 mg (ciprofloxacin equivalent) film-coated tablets. The inactive ingredients are starch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water. Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

CLINICAL PHARMACOLOGY

Cipro® tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Serum concentrations increase proportionately with the dose as shown:

Dose (mg)	Maximum Serum Concentration (µg/mL)	Area Under Curve (AUC) (µg • hr/mL)
250	1.2	4.8
500	2.4	11.6
750	4.3	20.2
1000	5.4	30.8

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 µg/mL, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours.

Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250 mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 µg/mL during the first two hours and are approximately 30 µg/mL at 8 to 12 hours after dosing. 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 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, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1-2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

When Cipro® is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that are closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See PRECAUTIONS.)

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. (See PRECAUTIONS.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See DOSAGE AND ADMINISTRATION.)

In preliminary studies in patients with stable chronic liver 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.

The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (See INDICATIONS AND USAGE section):

Gram-positive bacteria

Enterococcus faecalis
(Many strains are only moderately susceptible)

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative bacteria

Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae

Klebsiella pneumoniae
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii

Pseudomonas aeruginosa
Salmonella typhi
Serratia marcescens
Shigella flexneri
Shigella sonnei

Ciprofloxacin has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown.

Gram-positive bacteria

Staphylococcus haemolyticus
Staphylococcus hominis

Staphylococcus saprophyticus

Gram-negative bacteria

Acinetobacter calcoaceticus
subs. *anitratus*
Acinetobacter calcoaceticus
subs. *Iwoffii*
Aeromonas caviae
Aeromonas hydrophila
Brucella melitensis

Campylobacter coli
Edwardsiella tarda
Enterobacter aerogenes
Haemophilus ducreyi
Klebsiella oxytoca
Legionella pneumophila
Moraxella (Branhamella) catarrhalis

Neisseria meningitidis
Pasteurella multocida
Salmonella enteritidis
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

Other organisms

Chlamydia trachomatis (only moderately susceptible)
Mycobacterium tuberculosis (only moderately susceptible)

Most strains of *Pseudomonas cepacia* and some strains of *Xanthomonas (Pseudomonas) maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimum bactericidal concentration (MBC) generally does not exceed the minimum inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation).

Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

In vitro studies have shown that additive activity often results when ciprofloxacin is combined with other antimicrobial agents such as beta-lactams, aminoglycosides, clindamycin, or metronidazole. Synergy has been reported particularly with the combination of ciprofloxacin and a beta-lactam; antagonism is observed only rarely.

Susceptibility Tests

Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimates

of susceptibility of bacteria to antimicrobial agents. One such standardized procedure¹ which has been recommended for use with disks to test susceptibility of organisms to ciprofloxacin uses the 5- μ g ciprofloxacin disk. Interpretation involves correlation of the diameters obtained in the disk test with the minimum inhibitory concentrations (MICs) for ciprofloxacin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 5- μ g ciprofloxacin disk should be interpreted according to the following criteria:	Zone Diameter (mm)	Interpretation
	≥ 21	(S) Susceptible
	16 – 20	(I) Intermediate (Moderately Susceptible)
	≤ 15	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate (Moderately Susceptible)" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are attained. A report of "Resistant" indicates that achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Dilution Techniques: Use a standardized dilution method ² (broth, agar, microdilution) or equivalent with ciprofloxacin powder. The MIC values obtained should be interpreted according to the following criteria:	MIC (μg/mL)	Interpretation
	≤ 1	(S) Susceptible
	2	(I) Intermediate (Moderately Susceptible)
	≥ 4	(R) Resistant

Standardized procedures require the use of laboratory control organisms. This is true for both standardized diffusion techniques and standardized dilution techniques. The 5- μ g ciprofloxacin disk should give the following zone diameters and the standard ciprofloxacin powder should provide the following MIC values:

QC Strains	Disk Zone Diameter (mm)	MIC (μ g/mL)
<i>S. aureus</i> (ATCC 25923)	22 – 30	—
<i>S. aureus</i> (ATCC 29213)	—	0.12 – 0.5
<i>E. coli</i> (ATCC 25922)	30 – 40	0.004 – 0.015
<i>P. aeruginosa</i> (ATCC 27853)	25 – 33	0.25 – 1.0
<i>E. faecalis</i> (ATCC 29212)	—	0.25 – 2.0

For anaerobic bacteria the MIC of ciprofloxacin can be determined by agar or broth dilution (including microdilution) techniques³.

INDICATIONS AND USAGE

Cipro[®] is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, or *Enterococcus faecalis*.

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi*.

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Sexually Transmitted Diseases (See WARNINGS.)

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri** or *Shigella sonnei** when antibacterial therapy is indicated.

*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered.

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[®] may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. 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.

CONTRAINDICATIONS

Cipro® (ciprofloxacin hydrochloride) is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PRECAUTIONS-PEDIATRIC USE, PREGNANCY AND NURSING MOTHERS SUBSECTIONS.) 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.)

Convulsions have been reported in patients receiving ciprofloxacin. Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving drugs in this class. Quinolones may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion and hallucinations. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures. (See ADVERSE REACTIONS.)

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF 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.

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after three months.

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 steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

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.

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See DOSAGE AND ADMINISTRATION.)

Moderate to severe phototoxicity manifested by an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium, aluminum, or calcium, products containing iron, or multivitamins containing zinc. However, usual dietary intake of calcium has not been shown to alter the absorption of ciprofloxacin.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Patients should be advised to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to discontinue therapy if phototoxicity occurs.

Ciprofloxacin 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.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.

Drug Interactions: 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.

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.

Concurrent administration of ciprofloxacin with antacids containing magnesium, aluminum, or calcium; with sucralate or divalent and trivalent cations such as iron may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. To a lesser extent this effect is demonstrated with zinc-containing multivitamins. (See DOSAGE AND ADMINISTRATION for concurrent administration of these agents with ciprofloxacin.)

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

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

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.

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

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 V₇₉ 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)

Long term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy: Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See WARNINGS.)

ADVERSE REACTIONS

During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of patients treated, possibly related in 9.2% (total of 16.5% thought to be possibly or probably related to drug therapy), and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of patients treated, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin treated patients are listed below.

CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis

CENTRAL NERVOUS SYSTEM: dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia (See above.) (See PRECAUTIONS.)

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic jaundice has been reported.

MUSCULOSKELETAL: joint or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism

SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.)

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See WARNINGS.)

SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances nausea, vomiting, tremor, irritability or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In domestic clinical trials involving 214 patients receiving a single 250 mg oral dose, approximately 5% of patients reported adverse experiences without reference to drug relationship. The most common adverse experiences were vaginitis (2%), headache (1%), and vaginal pruritus (1%). Additional reactions, occurring in 0.3%-1% of patients, were abdominal discomfort, lymphadenopathy, foot pain, dizziness, and breast pain. Less than 20% of these patients had laboratory values obtained, and these results were generally consistent with the pattern noted for multi-dose therapy.

Other adverse events reported in the postmarketing phase include anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, jaundice, hepatic necrosis, toxic psychosis, postural hypotension, possible exacerbation of myasthenia gravis, anosmia, confusion, dysphasia, nystagmus, pseudomembranous colitis, pancreatitis, dyspepsia, flatulence, and constipation. Also reported were hemolytic anemia; agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; renal calculi; and change in serum phenytoin. (See PRECAUTIONS.)

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic — Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic — Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal — Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of patients treated were: Elevation of serum gamma-glutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis.

OVERDOSAGE

In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended adult dosage for Infectious Diarrhea or Typhoid Fever is 500 mg every 12 hours.

For the treatment of uncomplicated urethral and cervical gonococcal infections, a single 250 mg dose is recommended.

DOSAGE GUIDELINES

Type of Infection	Type or Severity	Unit Dose	Frequency	Daily Dose
Urinary tract	Mild/Moderate	250 mg	q 12 h	500 mg
	Severe/Complicated	500 mg	q 12 h	1000 mg
Lower respiratory tract; Bone and Joint;	Mild/Moderate	500 mg	q 12 h	1000 mg
	Severe/Complicated	750 mg	q 12 h	1500 mg
Skin or Skin Structure				
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q 12 h	1000 mg
Typhoid Fever	Mild/Moderate	500 mg	q 12 h	1000 mg
Urethral and Cervical Gonococcal Infections	Uncomplicated	250 mg	single dose	—

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

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Infectious Diarrhea may be treated for 5-7 days. Typhoid fever should be treated for 10 days.

Concurrent Use With Antacids or Multivalent Cations: Concurrent administration of ciprofloxacin with sucralate or divalent and trivalent cations such as iron or antacids containing magnesium, aluminum, or calcium may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. Therefore, concurrent administration of these agents with ciprofloxacin should be avoided. However, usual dietary intake of calcium has not been shown to alter the bioavailability of ciprofloxacin. Single dose bioavailability studies have shown that antacids may be administered either 2 hours after or 6 hours before ciprofloxacin dosing without a significant decrease in bioavailability. Histamine H₂-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

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. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment:

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

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

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 × the value calculated for men.

The serum creatinine should represent a steady state of renal function.

In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be administered at the intervals noted above; however, patients should be carefully monitored and the serum ciprofloxacin concentration should be measured periodically. Peak concentrations (1-2 hours after dosing) should generally range from 2 to 4 µg/mL.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

HOW SUPPLIED

Cipro® (ciprofloxacin hydrochloride) is available as round, slightly yellowish film-coated tablets containing 250 mg ciprofloxacin. The 250 mg tablet is coded with the word "Cipro" on one side and "250" on the reverse side. Cipro® is also available as capsule shaped, slightly yellowish film-coated tablets containing 500 mg or 750 mg ciprofloxacin. The 500 mg tablet is coded with the word "Cipro" on one side and "500" on the reverse side; the 750 mg tablet is coded with the word "Cipro" on one side and "750" on the reverse side. Available in bottles of 50's, 100's and in Unit Dose packages of 100.

	Strength	NDC Code	Tablet Identification
Bottles of 50:	750 mg	NDC 0026-8514-50	Cipro 750
Bottles of 100:	250 mg	NDC 0026-8512-51	Cipro 250
	500 mg	NDC 0026-8513-51	Cipro 500
Unit Dose Package of 100:	250 mg	NDC 0026-8512-48	Cipro 250
	500 mg	NDC 0026-8513-48	Cipro 500
	750 mg	NDC 0026-8514-48	Cipro 750

Store below 86°F (30°C).

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 beagles 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. 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.

In dogs, ciprofloxacin at 3 and 10 mg/kg by rapid IV injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid IV 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 fenbufen, 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.

References: 1. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7, NCCLS, Villanova, PA, April, 1990. 2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically-Second Edition. Approved Standard NCCLS Document M7-A2, Vol. 10, No. 8, NCCLS, Villanova, PA, April, 1990. 3. National Committee for Clinical Laboratory Standards, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria-Second Edition, Approved Standard NCCLS Document M11-A2, Vol. 10, No. 15, NCCLS, Villanova, PA, December, 1990.



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