PRODUCT MONOGRAPH

Pr CIPROFLOXACIN

(Ciprofloxacin Tablets, USP)

Tablets 250 mg, 500 mg, & 750 mg

Ciprofloxacin (as Ciprofloxacin Hydrochloride)

Antibacterial Agent

Manufactured by:
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Pr CIPROFLOXACIN

Ciprofloxacin Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	250, 500, & 750 mg tablets	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CIPROFLOXACIN (Ciprofloxacin Tablets, USP) may be indicated for the treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

Respiratory Tract Infections
Acute exacerbation of chronic bronchitis caused by:
Haemophilus influenzae
Moraxella catarrhalis

Acute pneumonia caused by:
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Staphylococcus aureus

Acute sinusitis caused by:
Haemophilus influenzae
Moraxella catarrhalis

Due to the nature of the underlying conditions which usually predispose patients to pseudomonas infections of the respiratory tract, bacterial eradications may not be achieved in patients who display clinical improvement despite evidence of *in vitro* sensitivity. In patients requiring

subsequent courses of therapy, CIPROFLOXACIN tablets should be used alternately with other antipseudomonal agents. Some strains of *Pseudomonas aeruginosa* may develop resistance during treatment. Therefore, susceptibility testing should be performed periodically during therapy to detect the emergence of bacterial resistance.

Urinary Tract Infections
Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis, pyelonephritis, and pyelitis caused by:

Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Morganella morganii
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus faecalis

Acute uncomplicated cystitis:
in females caused by *Eschericia coli*

Chronic Bacterial Prostatitis
Caused by:
Escherichia coli

Skin and Soft Tissue Infections
Caused by:
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes

Bone and Joint Infections
Caused by:
Enterobacter cloacae
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus

Infectious Diarrhea (when antibacterial therapy is indicated)
Caused by:
Campylobacter jejuni
Escherichia coli (enterotoxigenic strains)
Shigella dysenteriae
Shigella flexneri
Shigella sonnei

Meningococcal Carriers
Treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. An MIC determination on the isolate from the index case should be performed as soon as possible. **Ciprofloxacin is not indicated for the treatment of meningococcal meningitis.**

Typhoid Fever (enteric fever)
Caused by:
Salmonella paratyphi
Salmonella typhi

Uncomplicated Gonorrhea
Cervical/urethral/rectal/pharyngeal infections caused by *Neisseria gonorrhoea*. Because co-infection with *Chlamydia trachomatis* is common, consideration should be given to treating presumptively with an additional regimen that is effective against *C. trachomatis*.

Appropriate culture and susceptibility tests should be performed prior to initiating treatment in order to isolate and identify organisms causing the infection and to determine their susceptibilities to ciprofloxacin. Therapy with CIPROFLOXACIN tablets may be initiated before results of these tests are known. However, modification of this treatment may be required once results become available or if there is no clinical improvement. Culture and susceptibility testing performed periodically during therapy will provide information on the possible emergence of bacterial resistance. If anaerobic organisms are suspected to be contributing to the infection, appropriate therapy should be administered.

CONTRAINDICATIONS

CIPROFLOXACIN (Ciprofloxacin tablets, USP) is contraindicated in patients who have shown hypersensitivity to ciprofloxacin, or other quinolone antibacterial agents or any of the excipients.

Concurrent administration of ciprofloxacin and tizanidine is contraindicated since it may result in an undesirable increase in serum tizanidine concentrations. This can be associated with clinically relevant tizanidine-induced side effects (hypotension, somnolence, drowsiness).

WARNINGS AND PRECAUTIONS

General

The safety and efficacy of CIPROFLOXACIN (Ciprofloxacin tablets, USP) in children, adolescents (under the age of 18 years), pregnant women and nursing women have not been established. (See **Special Populations** below: **Pregnant Women, Nursing Women, and Pediatrics**)

Ability to Drive and Operate Machinery: Fluoroquinolones including ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions. This applies particularly in combination with alcohol (see **ADVERSE REACTIONS**).

***Streptococcus pneumonia* Infections:** Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae.*

Cardiovascular

Cardiac Disorders: Ciprofloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation of the QT interval (eg, class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (eg, known QT prolongation, uncorrected hypokalemia) (see **DRUG INTERACTIONS** and **ADVERSE REACTIONS**).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g., theophylline, methylxanthines, caffeine, duloxetine, clozapine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see **CONTRAINDICATIONS and DRUG INTERACTIONS).**

Endocrine and Metabolism

Disturbances of Blood Glucose: Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with the use of quinolones, including ciprofloxacin (see **ADVERSE REACTIONS**).

Gastrointestinal

Clostridium difficile-associated disease: Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including ciprofloxacin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and many permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*. Drugs that inhibit peristalsis may delay clearance of *C. difficile* and its toxins, and therefore should not be used in the treatment of CDAD. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Hepatic/Biliary/Pancreatic

In preliminary studies in patients with stable chronic liver cirrhosis (with mild to moderate hepatic impairment), no significant changes in ciprofloxacin pharmacokinetics were observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency and stable chronic cirrhosis (with severe hepatic impairment), however, have not been fully elucidated. An increased incidence of nausea, vomiting, headache and diarrhea were observed in this patient population (see **DETAILED PHARMACOLOGY, Human Pharmacology**).

Musculoskeletal

Myasthenia Gravis: Fluoroquinolones, including ciprofloxacin, 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 ciprofloxacin in patients with a known history of myasthenia gravis (see **ADVERSE**

REACTIONS).

Tendinitis: Rupture of the shoulder, hand and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin (see **ADVERSE REACTIONS).** Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. 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. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Ciprofloxacin 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.

Ciprofloxacin should not be used in patients with a history of tendon disease/disorder related to previous quinolone treatment.

Neurologic

CNS and Psychiatric Effects: Seizures and toxic psychoses may occur with quinolone therapy. Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychoses have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and rarely, suicidal thoughts or acts. In rare cases, depression or psychosis can progress to self-endangering behaviour. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. Ciprofloxacin should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold (see **ADVERSE REACTIONS**).

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 (see **ADVERSE REACTIONS**).

Renal

Crystalluria related to ciprofloxacin has been reported only rarely in man because human urine is usually acidic. Crystals have been observed in the urine of laboratory animals, usually from alkaline urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Since ciprofloxacin is eliminated primarily by the kidney, CIPROFLOXACIN tablets should be used with caution and at a reduced dosage in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION** and **DETAILED PHARMACOLOGY, Human Pharmacology**).

Sensitivity/Resistance

Hypersensitivity: Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving quinolone therapy, including ciprofloxacin (see **ADVERSE REACTIONS**). These reactions may occur within the first 30 minutes following the first dose and may require epinephrine and other emergency measures. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving therapy with all antibiotics. 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 (e.g., 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, hepatic necrosis with fatal outcome, anemia including hemolytic and aplastic, thrombocytopenia including thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities.

Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitization (i.e., sunburn-like skin reactions) occurs.

Prolonged use of CIPROFLOXACIN Tablets may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is therefore essential, and if superinfection should occur during therapy, appropriate measures should be taken.

Skin

Phototoxicity: Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight or ultraviolet light while receiving drugs in this class. Excessive exposure to sunlight or ultraviolet light should be avoided. Therapy should be discontinued if phototoxicity occurs.

Special Populations

Pregnant Women: The safety of ciprofloxacin hydrochloride in pregnancy has not yet been established. CIPROFLOXACIN Tablets should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus (see **WARNINGS AND PRECAUTIONS, General** above). Ciprofloxacin hydrochloride has been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing Women: Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from women taking ciprofloxacin, a decision should be made to discontinue nursing or to discontinue the administration of CIPROFLOXACIN, taking into account the importance of the drug to the mother and the possible risk to the infant (see **WARNINGS AND PRECAUTIONS, General** above)

Pediatrics: The safety and efficacy of ciprofloxacin in the pediatric population less than 18 years of age have not been established. Quinolones, including ciprofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species (see **WARNINGS AND PRECAUTIONS, and TOXICOLOGY**). Damage to juvenile weight-bearing joints and lameness were observed both in rat and dog studies but not in weaned piglets (see **TOXICOLOGY**). Histopathological examination of the weight-bearing joints in immature dogs revealed permanent lesions of the cartilage.

Geriatrics: Ciprofloxacin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function (see **DETAILED PHARMACOLOGY, Human Pharmacology**).

Theophylline

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions include cardiac arrest, seizure, status epilepticus and respiratory failure. Similar serious adverse events have been noted with administration of theophylline alone; however, the possibility that ciprofloxacin may potentiate these reactions cannot be eliminated. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Monitoring and Laboratory Tests

Interaction with Tests: Ciprofloxacin *in vitro* potency may interfere with the *Mycobacterium spp.* culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Ciprofloxacin hydrochloride tablets are generally well tolerated. During worldwide clinical investigation (1991), 16,580 courses of ciprofloxacin treatment were evaluated for drug safety. The incidence of adverse reactions was 8.0%. In orally treated patients enrolled in clinical trials, the most frequently reported events, possibly, probably drug-related were: nausea (1.3%), and diarrhea (1.0%).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Events possibly, probably drug-related occurring at a frequency of less than 1% with ciprofloxacin treatment during clinical trials and subsequent post-marketing surveillance are as follows:

Body as a Whole: back pain, chest pain, pain, pain in extremities, moniliasis.

Cardiovascular System: palpitation, phlebitis, tachycardia, thrombophlebitis. The following has been reported rarely ≥ 0.01% <0.1%): hypotension. The following have been reported very rarely (<0.01%): angina pectoris, atrial fibrillation, cardiac arrest, cerebrovascular disorder, electrocardiogram abnormality, hot flashes, hypertension, kidney vasculitis, myocardial infarct, pericarditis, pulmonary embolus, substernal chest pain, syncope (fainting), vasodilation (hot flashes).

Digestive: abdominal pain, anorexia, dry mouth, dyspepsia, dysphagia, enlarged abdomen, flatulence, gastrointestinal moniliasis, jaundice, stomatitis, vomiting, abnormal liver function test. The following have been reported rarely: moniliasis (oral), cholestatic jaundice, and pseudomembranous colitis. The following have been reported very rarely: constipation, esophagitis, gastrointestinal hemorrhage, glossitis, hepatomegaly, ileus, increased appetite,

intestinal perforation, life-threatening pseudomembranous colitis with possible fatal outcome, liver damage, melena, pancreatitis, tenesmus, tooth discoloration, toxic megacolon, ulcerative stomatitis.

Hemic and Lymphatic: agranulocytosis, anaemia, eosinophilia, granulocytopenia, leukocytopenia, leukocytosis, pancytopenia. The following have been reported very rarely: altered prothrombin levels, haemolytic anaemia, marrow depression (life threatening), pancytopenia (life threatening), thrombocytopenia, thrombocytosis.

Hypersensitivity: rash. The following have been reported rarely: allergic reaction, anaphylactic/anaphylactoid reactions including facial, vascular and laryngeal edema, drug fever, haemorrhagic bullae and small nodules (papules) with crust formation showing vascular involvement (vasculitis), hepatitis, interstitial nephritis, petechiae (punctuate skin hemorrhages), pruritus, serum sickness-like reaction, Stevens-Johnson syndrome (potentially life-threatening) (see **WARNINGS AND PRECAUTIONS**). The following have been reported very rarely: shock (anaphylactic; life-threatening), pruritic rash, erythema multiforme (minor), erythema nodosum, major liver disorders including hepatic necrosis, (very rarely progressing to life threatening hepatic failures), epidermal necrolysis (Lyell Syndrome, potentially life-threatening).

Metabolic and Nutritional Disorder: creatinine increased. The following have been reported rarely: edema (face) and hyperglycemia (see **WARNINGS AND PRECAUTIONS**).

Musculoskeletal: The following have been reported rarely in patients for all ages: achiness, arthralgia (joint pain), joint disorder (joint swelling), pain in the extremities, partial or completed tendon rupture (shoulder, hand or Achilles tendon), tendinitis (predominantly achillotendinitis), myalgia (muscular pain). The following have been reported very rarely: myasthenia (exacerbation of symptoms of myasthensia gravis) (see **WARNINGS AND PRECAUTIONS**).

Nervous System: agitation, confusion, convulsion, dizziness, hallucinations, headache, hypesthesia, increased sweating, insomnia, somnolence, tremor (trembling). The following has been reported rarely: paresthesia (peripheral paralgesia) (see **WARNINGS AND PRECAUTIONS**). The following have been reported very rarely: abnormal dreams (nightmares), anxiety, apathy, ataxia, depersonalization, depression, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, paresthesia, polyneuritis, sleep disorder, twitching, grand mal convulsions, abnormal (unsteady) gait, psychosis, intracranial hypertension. In some instances these reactions occurred after the first administration of ciprofloxacin. In these instances, ciprofloxacin has to be discontinued and the doctor should be informed immediately.

Other: The following have been reported rarely: asthenia (general feeling of weakness, tiredness), death.

Respiratory System: dyspnea. The following have been reported very rarely: hiccup, hyperventilation, increased cough, larynx edema, lung edema, lung hemorrhage, pharyngitis, stridor, voice alteration.

Skin/Appendages: pruritus, rash, maculopapular rash. The following has been reported rarely: photosensitivity reaction. The following have been reported very rarely: alopecia, angioedema, fixed eruption, photosensitive dermatitis, petechia, urticaria.

Special Senses: abnormal vision (visual disturbances), taste perversion, tinnitus. The following have been reported rarely: transitory deafness (especially at higher frequencies), taste loss (impaired taste). The following have been reported very rarely: chromatopsia, colour blindness, conjunctivitis, corneal opacity, diplopia, ear pain, eye pain, parosmia (impaired smell), anosmia (usually reversible on discontinuation).

Urogenital System: albuminuria, hematuria. The following have been reported rarely: abnormal kidney function, acute kidney failure, dysuria, leukorrhea, nephritis interstitial, urinary retention, vaginitis, vaginal moniliasis.

Laboratory Values: increased alkaline phosphatase, ALT increased, AST increased, BUN (urea) increased, cholestatic parameters increased, Gamma - GT increased, lactic dehydrogenase increased, NPN increased, transaminases increased, decreased albuminuria, bilirubinemia, creatinine clearance decreased, hypercholesteremia, hyperuricemia, increased sedimentation rate. The following have been reported rarely: acidosis, increased amylase, crystalluria, electrolyte abnormality, haematuria, hypercalcemia, hypocalcemia and lipase increased.

Most of the adverse events reported were described as only mild or moderate in severity.

The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide post-marketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and in all indications): arrhythmia, atrial flutter, bleeding diathesis, bronchospasm, *C. difficile* associated diarrhea, candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, delirium, drowsiness, dysphasia, edema (conjunctivae, hands, lips, lower extremities, neck), epistaxis, exfoliative dermatitis, fever, gastrointestinal bleeding, gout (flare up), gynecomastia, hearing loss, hemoptysis, hemorrhagic cystitis, hyperpigmentation, joint stiffness, lightheadedness, lymphadenopathy, manic reaction, myoclonus, nystagmus, pain (arm, breast, epigastric, foot, jaw, neck, oral mucosa), paranoia, peripheral neuropathy, phobia, pleural effusion, polyneuropathy, polyuria, postural hypotension, pulmonary embolism, purpura, QT prolongation, renal calculi, respiratory arrest, respiratory distress, restlessness, rhabdomyolysis, torsades de pointes, toxic psychosis, unresponsiveness, urethral bleeding, urination (frequent), ventricular ectopy, ventricular

fibrillation, ventricular tachycardia, vesicles, visual acuity (decreased) and visual disturbances (flashing lights, change in colour perception, overbrightness of lights).

DRUG INTERACTIONS

Drug-Drug Interactions

Class IA or III Antiarrhythmics: Precaution should be taken when using ciprofloxacin together with class IA or III antiarrhythmics as ciprofloxacin may have an additive effect on the QT interval (see **WARNINGS AND PRECAUTIONS**).

Clozapine: Following concomitant administration of 250 mg ciprofloxacin for 7 days, serum concentrations of clozapine and n-desmethylclozapine were increased by 29% and 31%, respectively (see **WARNINGS AND PRECAUTIONS**).

Cyclosporine: Some quinolones, including ciprofloxacin, have been associated with transient increases in serum creatinine levels in patients who are concomitantly receiving cyclosporine.

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 an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ferrous Sulfate: Oral ferrous sulfate at therapeutic doses decreases the bioavailability of oral ciprofloxacin, therefore concomitant therapy is not advised.

Glyburide: In particular cases, concurrent administration of ciprofloxacin and glyburide can intensify the action of glyburide (hypoglycemia).

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

Lidocaine: It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Ciprofloxacin may increase the systemic toxicity of lidocaine.

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 accelerates the absorption of ciprofloxacin (oral), resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Multivalent Cations: Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, polymeric phosphate binders such as sevelamer, lanthanum carbonate, sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, mineral supplements 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. Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.

NSAID: Concomitant administration of a nonsteroidal anti-inflammatory drug (fenbufen) with a quinolone (enoxacin) has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid: Probenecid blocks renal tubular secretion of ciprofloxacin and has been shown to produce an increase in the level of ciprofloxacin in the serum.

Ropinirole: In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Ciprofloxacin may increase the systemic toxicity of ropinirole.

Sildenafil: C_{max} and AUC of sildenafil were increased approximately two-fold in healthy subjects after an oral dose of 50 mg was given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used when prescribing ciprofloxacin concomitantly with sildenafil, taking into consideration the risks and the benefits.

Theophylline: 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. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Tizanidine: In a clinical study in healthy subjects there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with ciprofloxacin (see **CONTRAINDICATIONS**).

Vitamin K Antagonists: Simultaneous administration of ciprofloxacin with a vitamin K

antagonist may augment its anticoagulant effects. 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. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin and acenocoumarol).

Drug-Food Interactions

Caffeine and Other Xanthine Derivatives: Caffeine has been shown to interfere with the metabolism and pharmacokinetics of ciprofloxacin. Excessive caffeine intake should be avoided.

Upon concurrent administration of ciprofloxacin and pentoxifylline (oxpentifylline)-containing products, raised serum concentrations of this xanthine derivative were reported.

Food and Dairy Products: Although, ciprofloxacin may be taken with meals that include milk, simultaneous administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible. It is recommended that ciprofloxacin be administered at least 2 hours before or 2 hours after substantial calcium intake (>800 mg) (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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-defence mechanisms, and the status of renal function.

Recommended Dose and Dosage Adjustment

Adults

The recommended dosages of CIPROFLOXACIN tablets are:

Table 1: Recommended Dosages for CIPROFLOXACIN

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Mild/Moderate	250 mg	q12h	500 mg
	Severe/Complicated	500 mg	q12h	1000 mg
Chronic Bacterial Prostatitis	Asymptomatic/Mild/Moderate	500 mg	q12h	1000 mg
Respiratory Tract Bone & Joint Skin & Soft Tissue	Mild/Moderate	500 mg	q12h	1000 mg
	Severe*/Complicated	750 mg	q12h	1500 mg
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q12h	1000 mg
Urogenital and Extragenital Gonorrhea	Uncomplicated	500 mg	Once	500 mg
Typhoid Fever	Mild/Moderate	500 mg	q12h	1000 mg
Neisseria meningitidis Nasopharyngeal colonization	Carrier State	750 mg	Once	750 mg
Acute Sinusitis	Moderate	500 mg	q12h	1000mg

* e.g., hospital-acquired pneumonia, osteomyelitis

Depending on the severity of the infections, as well as the clinical and bacteriological responses, the average treatment period should be approximately 7 to 14 days. Generally, treatment should last 3 days beyond the disappearance of clinical symptoms or until cultures are sterile. Patients with osteomyelitis may require treatment for a minimum of 6 to 8 weeks and up to 3 months. With acute cystitis in females a 3 to 5 day treatment may be sufficient. With infectious diarrhea a five-day treatment may be sufficient. Typhoid fever should be treated for 14 days. Acute sinusitis should be treated for 10 days with 500 mg q 12h. Chronic bacterial prostatitis should be treated for 28 days with 500 mg q 12h.

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. (See **DETAILED PHARMACOLOGY, Human Pharmacology**). This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides a guideline for dosage adjustment of ciprofloxacin hydrochloride tablets. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments.

Table 2: Maximum Daily Dose with Stated Creatinine Clearance or Serum Creatinine

Creatinine Clearance mL/min/1.73m^2	Maximum Daily Dose	Serum Creatinine Concentration mg/100mL
	Oral	
31-60	1000 mg	1.4-1.9
≤ 30	500 mg	≥ 2.0

Maximum daily doses are not to be exceeded when either creatinine clearance or serum creatinine are in the ranges stated.

Hemodialysis
Only a small amount of ciprofloxacin (< l0%) is removed from the body after hemodialysis or peritoneal dialysis. For hemodialysis patients, please follow dosing recommendations as described in Table 2. On dialysis days, the dose should be administered after dialysis.

When only the serum creatinine concentration is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function:

Creatinine Clearance mL/sec =

Males: $\frac{\text{Weight (kg) x (140 - age)}}{\text{49 x serum creatinine (µmol/L)}}$

Females: 0.85 x the above value

In traditional units mL/min=

Males: $\frac{\text{Weight (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/100 mL)}}$

Females: 0.85 x the above value

Impaired Hepatic Function
No dosage adjustment is required.

Pediatric Use
The safety and efficacy of ciprofloxacin hydrochloride tablets in individuals less than 18 years of age has not been established. CIPROFLOXACIN should not be used in pediatric patients and adolescents (see **WARNINGS AND PRECAUTIONS**).

Administration
CIPROFLOXACIN (Ciprofloxacin tablets, USP) may be taken before or after meals. Absorption is faster on an empty stomach. Patients should be advised to drink fluids liberally and avoid taking dairy products or antacids containing magnesium or aluminum.

Ciprofloxacin should be administered at least 2 hours before or 6 hours after antacids and mineral supplements containing magnesium or aluminum, as well as sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. (See **DRUG INTERACTIONS**)

Although ciprofloxacin may be taken with meals that include milk, simultaneous administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible. It is recommended that ciprofloxacin be administered at least 2 hours before or 2 hours after substantial calcium intake (>800 mg). (See **DRUG INTERACTIONS**)

OVERDOSAGE

In the event of acute, excessive oral overdosage, reversible renal toxicity, arthralgia, myalgia and CNS symptoms have been reported. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer magnesium- or calcium-containing antacids which reduce the absorption of ciprofloxacin and to maintain adequate hydration. Based on information obtained from subjects with chronic renal failure, only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic ciprofloxacin exposure.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Ciprofloxacin, a synthetic fluoroquinolone, has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Its bactericidal action is achieved through inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination.

Ciprofloxacin retained some of its bactericidal activity after inhibition of RNA and protein synthesis by rifampin and chloramphenicol, respectively. These observations suggest ciprofloxacin may possess two bactericidal mechanisms, one mechanism resulting from the inhibition of DNA gyrase and a second mechanism which may be independent of RNA and protein synthesis.

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to these other classes of antimicrobial agents (see **MICROBIOLOGY**). There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

Pharmacokinetics

(See **DETAILED PHARMACOLOGY, Human Pharmacology**)

Absorption: Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.

The absolute bioavailability is approximately 70-80%. Maximum serum concentrations (C_{max}) and total areas under serum concentration vs. time curves (AUC) increased in proportion to dose.

Distribution: The protein binding of ciprofloxacin is low (20-30%), and the substance is present in plasma largely in a non-ionized form. Ciprofloxacin can diffuse freely into the extravascular space. The large steady-state volume of distribution of 2-3 L/kg body weight shows that ciprofloxacin penetrates in tissues resulting in concentrations which clearly exceed the corresponding serum levels.

Metabolism: Small concentrations of four metabolites have been reported. They were identified as desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). M1 to M3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M4, with the smallest quantity, is largely equivalent to norfloxacin in its antimicrobial activity.

Excretion: Ciprofloxacin is largely excreted unchanged both renally and to a smaller extent non-renally. Renal clearance is between 0.18 to 0.3 L/h/kg and the total body clearance between 0.48 to 0.60 L/h/kg. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.

Non-renal clearance of ciprofloxacin is mainly due to active transintestinal secretion as well as metabolization. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

STORAGE AND STABILITY
Store between 15°C and 30°C

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms :

CIPROFLOXACIN (Ciprofloxacin Tablets, USP) 250 mg	Each white to off-white round, biconvex, film-coated tablet, embossed "$\frac{CR}{250}$" on one side and "□" on the other side, contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin. PVC/PE/PVDC film and aluminum foil unit dose blisters of 10's cartons of 100 (tablets), HDPE bottles of 100's and 500's
CIPROFLOXACIN (Ciprofloxacin Tablets, USP) 500 mg	Each white to off-white, capsule shaped, biconvex, film-coated tablet, embossed "CR 500" on one side and "□" on the other side, contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin. PVC/PE/PVDC film and aluminum foil unit dose blisters of 10's cartons of 100 (tablets), HDPE bottles of 100's and 500's.
CIPROFLOXACIN (Ciprofloxacin Tablets, USP) 750 mg	Each white to off-white, capsule shaped, bioconvex, film-coated tablet, embossed "CR 750" on one side and "□" on the other side, contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin. PVC/PE/PVDC film and aluminum foil unit dose blisters of 10's cartons of 100 (tablets), HDPE bottles of 50's and 100's

Composition:

Ciprofloxacin Hydrochloride, colloidal silicon dioxide, corn starch, crospovidone, magnesium stearate, microcrystalline cellulose, polyethyleneglycol, polyvinyl alcohol, pregelatinized starch, talc, and titanium dioxide

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

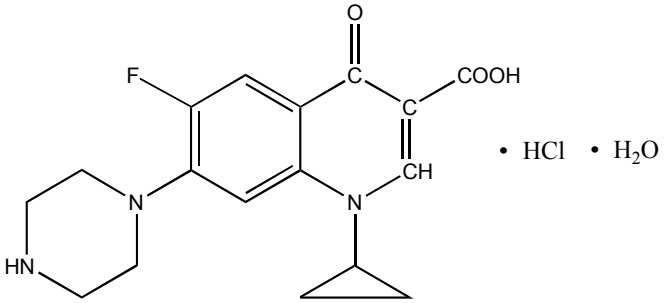
Drug Substance

Proper name: Ciprofloxacin hydrochloride, USP

Chemical name: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperzinyl)-3-quinolinecarboxylic acid hydrochloride monohydrate

Molecular formula and molecular mass: $C_{17}H_{18}FN_3O_3HCl\ H_2O$; 385.8

Structural formula:



Physicochemical properties: Ciprofloxacin hydrochloride is a pale yellow crystalline powder. Sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in acetone, in ethyl acetate, and in methylene chloride.

pH solubility profile:	pH	Solubility
	1	12 mg/mL
	2	36 mg/mL
	3	39 mg/mL
	4	42 mg/mL
	5	36 mg/mL
	6	38 mg/mL
	7	38 mg/mL
	8	38 mg/mL

pH and pKa values:	pH of a 2.5% solution in water is 3.0-4.5 The pKa_1 is 6.1 and the pKa_2 is 8.7
Melting Point:	318 – 320 °C

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study under fasting conditions was performed on CIPROFLOXACIN against the Canadian Reference Product, Cipro® (Bayer Inc.). The study was a blinded, single-dose, randomized, two-way cross-over, bioequivalence study on two formulations of the 750 mg ciprofloxacin tablets. The pharmacokinetic data are presented in the following table.

Two-way, Crossover
Single Dose (1 x 750 mg)
Fasted Study from Measured Data on Ciprofloxacin

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test†	Reference*	% Ratio of Geometric Means
AUC_T (ng.h/mL)	16020 16293 (19)	15219 15437 (17)	105
AUC_I (ng.h/mL)	16196 16468 (19)	15390 15607 (17)	105
C_{MAX} (ng/mL)	2930 2982 (20)	2851 2877 (14)	103
[1]T_{MAX} (h)	1.33 (31)	1.34 (34)	
[1]$T_{½}$ (h)	5.71 (11)	5.77 (12)	

† Ciprofloxacin 750 mg (Cobalt Pharmaceuticals Inc., Canada)
* Cipro® 750 mg manufactured by Bayer Inc., Canada. Purchased in Canada.
[1] expressed as arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Animal Pharmacology

Effects on Histamine Release

Ciprofloxacin was administered intravenously to 9 anaesthetized dogs (initially with thiopental sodium at 25 mg/kg i.v., followed by continuous infusion of a mixture of fentanyl 0.04 mg/kg/hr and dehydrobenzperidol 0.25 mg/kg/hr) at a single dose of 3, 10 or 30 mg/kg. Ciprofloxacin treatment resulted in circulatory changes similar to those caused by histamine release. These

were reductions in blood pressure, cardiac output and maximum rate of pressure increase in the left ventricle (dp/dt_{max}), and increase in heart rate. This histamine-liberating effect was counteracted by the simultaneous intravenous administration of 0.01 mg/kg pyrilamine maleate. No signs of histamine liberation were observed on conscious animals.

In vitro experiments on isolated rat mast cells also indicate that ciprofloxacin at concentrations of 0.1 to 100 mg/L has histamine liberating properties.

Bronchodilatory Effects
Ciprofloxacin was tested on isolated guinea-pig trachea at concentrations of 0.0001 to 10 mg/L. It produced a dose-related small but significant relaxation of respiratory airway smooth muscle. It has, however, no effect on leukotriene D4 and histamine-induced contractions at these doses.

CNS Effects
Ciprofloxacin was administered orally to 4 groups of 1 cat each under chloralose-urethane anaesthesia at doses of 0, 10, 20 and 100 mg/kg. No effects were observed on neuromuscular transmission, flexor reflex, or blood pressure.

Gastrointestinal Effects
Ciprofloxacin was administered orally to 4 groups of 20 mice each at doses of 0, 10, 30, and 100 mg/kg, 40 minutes prior to a 15% charcoal suspension. No effect was observed in intestinal charcoal transit time. When given to 3 groups of 20 rats each at doses of 0, 30 or 100 mg/kg, no gastric lesions were observed on sacrificing the animals after 5 hours.

When given intraduodenally to 3 groups of 8 rats each at doses of 0, 10 and 100 mg/kg, no increase in basal gastric acid secretion was observed on perfusion of the stomach.

Effect on Blood Glucose and Serum Triglycerides
Four groups of six fasting rats each were given intravenous injections of 0, 3, 10, and 30 mg/kg respectively. A slight but significant increase in blood glucose concentrations 60 minutes and 240 minutes post dose was observed in the 3 and 10 mg/kg groups but not in the 30 mg/kg group in comparison to controls.

At 60 minutes post dose, the serum triglyceride concentrations were slightly but significantly reduced in all three groups. This effect was not dose-related. At 120 minutes, the concentration was slightly elevated in the 30 mg/kg group.

Human Pharmacology

Pharmacokinetics
The relative bioavailability of oral ciprofloxacin, given as a tablet, is between 70 and 80 per cent compared to an equivalent dose of IV ciprofloxacin.

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets respectively to groups of 3 healthy male volunteers (age: 22.8 ± 3.5 years, weight: 68.5 ± 9.4 kg), ciprofloxacin was absorbed rapidly and extensively from the gastrointestinal tract.

Maximum serum concentrations (C_{max}) increased dose-proportionally and were attained 1 to 2 hours after oral dosing. The total areas under the serum concentration-time curves (AUC) were also increased in proportion to dose. Mean concentrations 12 hours after dosing with 250 mg, 500 mg, or 750 mg were 0.1, 0.2, and 0.4 mg/L, respectively. The serum elimination half-lives ($t_{½}$) were between 4 and 6 hours. (See Table 3 and Figure 1.)

Table 3: Pharmacokinetic Parameters Following a Single Oral Dose of Ciprofloxacin Tablets in Healthy Volunteers

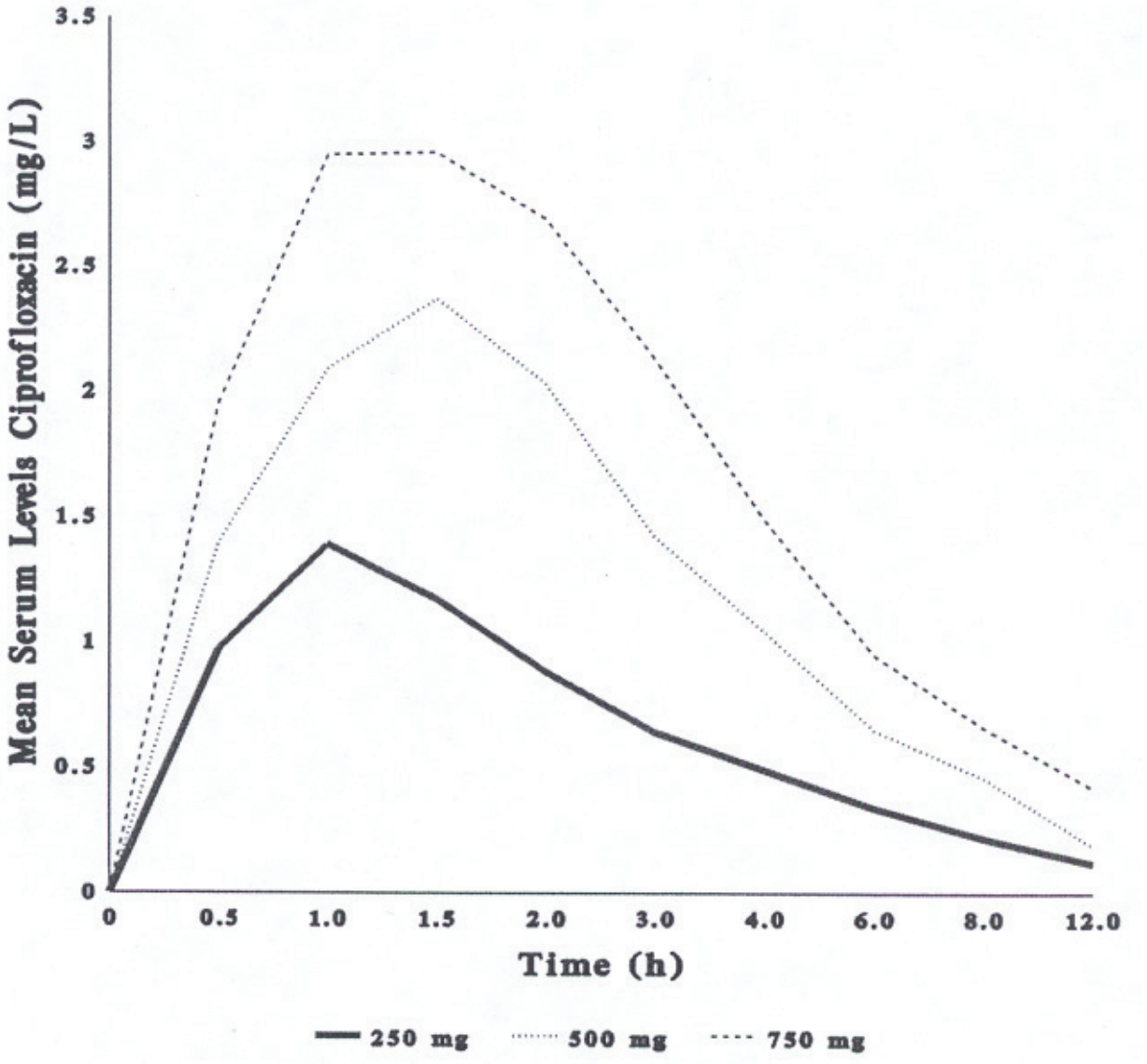
Dose	250 mg	500 mg	750 mg
C_{max} (mg/L)	1.42	2.60	3.41
$T_{½}$ (hr)	4.19	4.87	5.34
$AUG_{0-\infty}$ (mg•h/L)	5.43	10.60	15.03
t_{max} (hr)	1.11	1.11	1.56

Similar values were obtained following the oral administration of multiple doses every 12 hours for 7 days (see Table 4).

Table 4: Mean Pharmacokinetic Parameters of Ciprofloxacin at Steady State in Healthy Volunteers

Regimen	AUC_{0-12} (mg.h/L)	C_{max} (mg/L)	T_{max} (h)
Ciprofloxacin 500 mg PO q12h	13.7	2.97	1.23

Figure 1: Mean Ciprofloxacin Serum Concentration After Single Oral Doses



Tablets

Metabolism and Excretion
Ciprofloxacin is largely excreted unchanged both renally and, to a small extent, extra-renally. Small concentrations of 4 metabolites have been reported: Desethyleneciprofloxacin (M_1) (1.8%), sulphociprofloxacin (M_2) (5.0%), oxociprofloxacin (M_3) (9.6%) and formylciprofloxacin (M_4) (0.1%).

Following the oral administration of a single 259 mg dose of ^{14}C-labelled ciprofloxacin to six healthy male volunteers (age: 25.0 ± 1.46 years, weight: 70.0 ± 3.39 kg), approximately 94% of the dose was recovered in the urine and feces over five days. Most of the radioactivity was recovered in the urine (55.4%). Unchanged ciprofloxacin was the major radioactive moiety identified in both urine and feces, accounting for 45% and 25% of the dose, respectively. Total (urine and feces) excretion of all metabolites was 18.8%.

Table 5 shows urinary recovery data from another trial where healthy subjects were administered a single dose of ciprofloxacin in tablet form.

Table 5: Mean Urinary Excretion of Ciprofloxacin

Hours After Oral Administration of a Single Tablet				
	0 – 2	**2 – 4**	**4 – 8**	**8 – 12**
Urine Concentration mg/mL (±S.D.)				
250 mg po	205 (±89)	163 (±145)	101 (±65)	32 (±28)
500 mg po	255 (±204)	358 (±206)	117 (±86)	26 (±10)
750 mg po	243 (±143)	593 (±526)	169 (±131)	55 (±36)
Amount Excreted mg (±S.D.)				
250 mg dose	54.38 (±36.22)	26.79 (±11.78)	22.84 (±6.79)	8.90 (±4.25)
500 mg dose	64.51 (±25.06)	47.37 (±15.65)	39.54 (±11.17)	15.52 (±5.39)
750 mg dose	68.90 (±41.85)	72.43 (±33.13)	61.07 (±21.68)	28.11 (±7.64)

Factors Influencing the Pharmacokinetics

Age (Elderly)
In 4 females and 6 males, (age: 67 ± 4 years, weight: 65 ± 6 kg) with normal renal function for their age, given a single oral dose of 250 mg, maximum ciprofloxacin serum concentrations and areas under the serum concentration time curves were significantly higher than in 10 male younger volunteers (age: 24 ± 3 years, weight: 72 ± 9 kg). The time to peak serum concentrations, overall elimination half-life and urinary recovery of ciprofloxacin were similar in both age groups.

Table 6: Comparison of Pharmacokinetic Parameters between Healthy Elderly and Healthy Younger Volunteers Following Oral Administration of a Single 250 mg Tablet

Parameter	Elderly Volunteers (mean ± S.D.)	Younger Volunteers (mean ± S.D.)
C_{max} (mg/L)	1.8 ± 0.5	1.3 ± 0.4
t_{max} (hr)	1.2 ± 0.3	1.2 ± 0.1
t½ (hr)	3.7 ± 0.9	3.3 ± 0.6
Total AUC (mg·h/L)	7.25 ± 2.45	5.29 ± 1.21
% Dose Urinary Recovery after 24 hours	43	43

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. This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

The pharmacokinetics of ciprofloxacin following a single oral dose of 250 mg in 6 patients (5 male, 1 female, age: 51 ± 9 years) with normal renal function (see Group I, Table 7) were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment (see Group II, Table 7) and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis (see Group III, Table 7). Patients with renal insufficiency had significantly increased AUCs, prolonged (about 2-fold) elimination half-lives, and decreased renal clearances.

Haemodialysis resulted in a minimal decrease in plasma levels. From the dialysate concentrations, it can be estimated that no more than 2% of the dose was removed by dialysis over 4 hours, which was less than the amount lost in the urine over 24 hours in patients of Group II (see Table 7).

Table 7: Mean Pharmacokinetic Parameters for Ciprofloxacin Following Oral Administration of a Single 250 mg Tablet in Healthy Volunteers and in Patients with Renal Insufficiency

Group	Creatinine Clearance (mL/s/1.73 m^2) (mL/min/1.73 m^2)	Parameter					
		C_{max} (mg/L)	t_{max} (h)	Half-Life (h)	Total AUC (mg·h/mL)	Renal Clearance (mL/min)	% Dose Urinary Recovery (0-24 h)
I	>1.0 (>60)	1.52 (±0.21)	1.0 (±0.0)	4.4 (±0.2)	6.94 (±0.97)	232.9 (±44.8)	37.0 (±3.7)
II	<0.33 (<20)	1.70 (±0.41)	1.7 (±0.5)	8.7 (±0.9)	14.36 (±3.5)	18.3 (±3.5)	5.3 (±1.7)
III	End-Stage Renal Failure Treated by Hemodialysis	2.07 (±0.23)	1.6 (±0.2)	5.8 (±0.9)	15.87 (±2.0)		

Hepatic Impairment

In studies in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment), no significant changes in ciprofloxacin pharmacokinetics have been observed. In a study of 7 cirrhotic patients and healthy volunteers given ciprofloxacin 750 mg every 12 hours for a total of nine doses followed by a 1 week washout and then a 30 minute infusion of ciprofloxacin I.V. 200 mg, there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

Food

The administration of ciprofloxacin with food delayed absorption, as shown by an increase of approximately 50% in time to peak concentrations, but did not cause other changes in the pharmacokinetics of ciprofloxacin.

Theophylline

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.

Caffeine and Other Xanthine Derivatives

Ciprofloxacin decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration.

Upon concurrent administration of ciprofloxacin and pentoxifylline (oxpentifylline)-containing products, raised serum concentrations of this xanthine derivative were reported.

Class IA or III Antiarrhythmics
Precaution should be taken when using ciprofloxacin together with class IA or III antiarrhythmics as ciprofloxacin may have an additive effect on QT interval (see **WARNINGS AND PRECAUTIONS**).

Multivalent Cations
Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, lanthanum carbonate, sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, mineral supplements or products containing calcium, iron, or zinc.

Probenecid
Co-administration of probenecid (1000 mg) with ciprofloxacin (500 mg) orally resulted in about 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation.

Clozapine
Following concomitant administration of 250 mg ciprofloxacin for 7 days, serum concentrations of clozapine and n-desmethylclozapine were increased by 29% and 31%, respectively (see **WARNINGS AND PRECAUTIONS**).

Lidocaine
It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Ciprofloxacin may increase the systemic toxicity of lidocaine.

Ropinirole
In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in C_{max} and AUC of ropinirole of 60% and 84%, respectively. Ciprofloxacin may increase the systemic toxicity of ropinirole.

Sildenafil
C_{max} and AUC of sildenafil were increased approximately two-fold in healthy subjects after an oral dose of 50 mg was given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil, taking into consideration the risks and the benefits.

Vitamin K Antagonists
Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anticoagulant effects. 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. The INR should be monitored frequently during and

shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin and acenocoumarol).

Serum Protein Binding

Serum protein binding of ciprofloxacin is between 19% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs.

Tissue Concentrations

In one study, the apparent volume of distribution (Vd_{area}) of ciprofloxacin was estimated from the kinetic data recorded after oral doses and found to be approximately 3.5 L/kg, which suggests substantial tissue penetration.

The distribution of ciprofloxacin was observed to be rapid in healthy volunteers receiving various single and multiple intravenous doses. Fitting the serum profile to a two compartment model provides a distribution phase with a half-life between 0.2 and 0.4 hours. The volume of distribution at steady state (Vd_{SS}) and Vd_{area} were between 1.7 and 2.7 L/kg respectively. The volume of the central compartment was between 0.16 and 0.63 L/kg, which approximates the total volume of extracellular water.

Single intravenous doses of 100, 150, and 200 mg ciprofloxacin were administered to nine healthy volunteers to determine the excretion and distribution of ciprofloxacin following intravenous administration and to assess the effect of dose size on pharmacokinetic parameters.

Analysis with a three-compartmental pharmacokinetic model quantified approximate sizes and kinetics of distribution into two peripheral compartments: a rapidly equilibrating compartment (V_2) with a high intercompartmental clearance rate, accounting for the rapid decline in ciprofloxacin concentrations in serum immediately following drug infusion; and a second, slowly equilibrating tissue compartment with relatively slow intercompartmental clearance. This would contribute to the prolonged terminal half-life (4 to 5 h) of ciprofloxacin I.V.

The results of this study were as follows: volume of distribution at steady state (V_{ss}) was determined to be between 2.0 and 2.9 L/kg. Volumes in each compartment were determined to be: central compartment 0.2 - 0.4, peripheral V_2 0.6 - 0.8 and peripheral V_3 1.2 - 1.6 L/kg. Table 8 summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

Table 8: Distribution of Ciprofloxacin in Human Tissue/Fluid

Tissue/Fluid	No. of Patients	Single Dose of Ciprofloxacin	Peak Concentration (mg/kg or mg/L)	Mean Serum Concentration (mg/L)	Time After Dose (hr)
Skin Blister Fluid	6	500 mg po	1.4 ± 0.36	2.3 ± 0.7	1 – 6
Bone	4	750 mg po	1.4 ± 1.0	2.9 ± 2.2	2 – 4
Gynecological Tissue	18	500 mg po	1.3 ± 0.66 to 1.6 ± 0.97	1.4 ± 0.87	2 – 4
Prostatic Tissue	1	500 mg po	3.76	1.84	2.5
Muscle	4	250 mg po	2.4 ± 1.0	2.9 ± 2.2	2 – 4
Nasal Secretions	20	500 mg po	1.4 ± 0.81	1.8 ± 0.48	1 – 3

MICROBIOLOGY

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

Drug Resistance
The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other fluoroquinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *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 1×10^{-6}.

Activity *in vitro* and *in vivo*
Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. Ciprofloxacin is slightly less active when tested at acidic pH. The inoculums size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)

Staphylococcus saprophyticus
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Serratia marcescens
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei

The following *in vitro* data are available, **but their clinical significance is unknown.** Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trails.

Aerobic gram-positive microorganisms

Staphylococcuc haemolyticus
Staphylococcus hominis

Aerobic gram-negative microorganisms

Acetinobacter iwoffii
Aeromonas hydrophila
Edwardsiella tarda
Enterobacter aerogenes
Legionella pneumophila
Pasteurella multocida
Salmonella enteritidis
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

Most strains of *Burkholderia cepacia*, and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Susceptibility Testing

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.

Standardized procedures are based on a dilution method (1) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 9:

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (2) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 µg ciprofloxacin disk should be interpreted according to the criteria outlined in Table 9.

Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

Table 9: Susceptibility Interpretative Criteria for Ciprofloxacin

	MIC (µg/mL)			Zone Diameter (mm)		
Species	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriacae	≤ 1	2	≥ 4	≥ 21	16-20	≤ 15
Enterococcus faecalis	≤ 1	2	≥ 4	≥ 21	16-20	≤ 15
Methicillin susceptible *Staphylococcus* species	≤ 1	2	≥ 4	≥ 21	16-20	≤ 15
Pseudomonas aeruginosa	≤ 1	2	≥ 4	≥ 21	16-20	≤ 15
Haemophilus influenzae	≤ 1[a]	[g]	[g]	≥ 21[b]	[g]	[g]
Haemophilus parainfluenzae	≤ 1[a]	[g]	[g]	≥ 21[b]	[g]	[g]
Streptococcus pyogenes	≤ 1[c]	2[c]	≥ 4[c]	≥ 21[d]	16 – 20[d]	≤ 15[d]
Neisseria gonorrhoeae	≤ 0.06[e]	0.12 – 0.15[e]	≤ 1[e]	≥ 41[f]	28 – 40[f]	≤ 27[f]

Abbreviations: I = Intermediate; MIC = minimum inhibitory concentration; µg = microgram; mL = milliliter; mm = millimiter; R = Resistant; S = Susceptible

[a] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM). (1)

[b] This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM). (2)

[c] These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

[d] These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

[e] This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined growth supplement.

[f] This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement.

[g] The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. 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 which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control: Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For dilution technique, standard ciprofloxacin powder should provide the MIC values according to criteria outlined in Table 10. For diffusion technique, the 5 µg ciprofloxacin disk should provide the zone diameters outlined in Table 10.

Table 10: Quality Control for Susceptibility Testing

Strains	MIC Range (µg/mL)	Zone Diameter (mm)
Enterococcus faecalis ATCC 29212	0.25 – 2	-
Escherichia coli ATCC 25922	0.004 - 0.015	30 – 40
Haemophilus influenzae ATCC 49247	0.004 - 0.03[a]	34 – 42[d]
Pseudomonas aeruginosa ATCC 27853	0.25 – 1	25 – 33
Staphylococcus aureus ATCC 29213	0.12 – 0.5	-
Staphylococcus aureus ATCC 25923	-	22 – 30
Neisseria gonorrhoeae ATCC 49226	0.001 – 0.008[b]	48 – 58[e]
C. jejuni ATCC 33560	0.06 – 0.25 and 0.03 – 0.12[c]	-

Abbreviations: ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration; µg = microgram; mL = milliliter; mm = millimiter

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM). (1)

[b] *N. gonorrhoeae* ATCC 49226 tested by agar dilution procedure using GC agar and 1% defined growth supplement in a 5% CO_2 environment at 35-37°C for 20-24 hours.(2)

[c] *C. jejuni* ATCC 33560 tested by broth microdilution procedure using cation adjusted Mueller Hinton broth with 2.5-5% lysed horse blood in a microaerophilic environment at 36-37°C for 48 hours and for 42°C at 24 hours, respectively.

[d] These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM). (2)

[e] These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

TOXICOLOGY

Acute Toxicity

Species	Mode of Administration	LD_{50} (mg/kg)
Mouse	p.o.	approx. 5000
Rat	p.o.	approx. 5000
Rabbit	p.o.	approx. 2500
Mouse	i.v.	approx. 290
Rat	i.v.	approx. 145
Rabbit	i.v.	approx. 125
Dog	i.v.	approx. 250

Chronic Toxicity

Subacute Tolerability Studies over 4 Weeks

Oral administration: Doses up to and including 100 mg/kg were tolerated without damage by rats. Pseudoallergic reactions due to histamine release were observed in dogs.

Parenteral administration: In the highest-dose group in each case (rats 80 mg/kg and monkeys 30 mg/kg), crystals containing ciprofloxacin were found in the urine sediment. There were also changes in individual renal tubules, with typical foreign-body reactions dues to crystal-like precipitates. These changes are considered secondary inflammatory foreign-body reactions due to the precipitation of a crystalline complex in the distal renal tubule system.

Subchronic Tolerability Studies over 3 Months

Oral administration: All doses up to and including 500 mg/kg were tolerated without damage by rats. In monkeys, crystalluria and changes in the renal tubules were observed in the highest-dose group (135 mg/kg).

Parenteral administration: Although the changes in the renal tubules observed in rats were in some cases very slight, they were present in every dose group. In monkeys they were found only in the highest-dose group (18 mg/kg) and were associated with slightly reduced erythrocyte counts and hemoglobin values.

Chronic Tolerability Studies over 6 Months

Oral administration: Doses up to and including 500 mg/kg and 30 mg/kg were tolerated without damage by rats and monkeys, respectively. Changes in the distal renal tubules were again observed in some monkeys in the highest-dose group (90 mg/kg).

Parenteral administration: In monkeys slightly elevated urea and creatinine concentrations and changes in the distal renal tubules were recorded in the highest-dose group (20 mg/kg).

Carcinogenicity
In carcinogenicity studies in mice (21 months) and rats (24 months) with doses up to approximately 1000 mg/kg bw/day in mice and 125 mg/kg bw/day in rats (increased to 250 mg/kg bw/day after 22 weeks), there was no evidence of a carcinogenic potential at any dose level.

Reproduction Toxicology
Fertility studies in rats: Fertility, the intrauterine and postnatal development of the young, and the fertility of F1 generation were not affected by ciprofloxacin.

Embryotoxicity studies: These yielded no evidence of any embryotoxic or teratogenic action of ciprofloxacin.

Perinatal and postnatal development in rats: No effects on the perinatal or postnatal development of the animals were detected. At the end of the rearing period histological investigations did not bring to light any sign of articular damage in the young.

Mutagenicity
Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin. 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)
Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte Primary Culture DNA Repair Assay (LIDS) (Positive)

Two of the eight tests were positive, but results of the following four *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)

Dominant Lethal Test (Mice)
Chinese Hamster Bone Marrow

Special Tolerability Studies
It is known from comparative studies in animals, both with the older gyrase inhibitors and the more recent ones, that this substance class produces a characteristic damage pattern. Kidney damage, cartilage damage in weight-bearing joints of immature animals, and eye damage may be encountered.

Renal Tolerabilitv: The crystallization observed in the animal studies occurred preferentially under pH conditions that do not apply in man.

Compared to rapid infusion, a slow infusion of ciprofloxacin reduces the danger of crystal precipitation.

The precipitation of crystals in renal tubules does not immediately and automatically lead to kidney damage. In the animal studies, damage occured only after high doses, with correspondingly high levels of crystalluria. For example, although they always caused crystalluria, even high doses were tolerated over 6 months without damage and without foreign-body reactions occurring in individual distal renal tubules.

Damage to the kidneys without the presence of crystalluria has not been observed. The renal damage observed in animal studies must not, therefore, be regarded as a primary toxic action of ciprofloxacin on the kidney tissue, but as typical secondary inflammatory foreign-body reactions due to the precipitation of a crystalline complex of ciprofloxacin, magnesium, and protein.

Articular tolerabilitv studies: As it is also known for other gyrase inhibitors, ciprofloxacin causes damage to the large, weight-bearing joints in immature animals.

The extent of the cartilage damage varies according to age, species, and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions.

Retina tolerability studies: Ciprofloxacin binds to the melanin containing structures including the retina. Potential effects of ciprofloxacin on the retina were assessed in various pigmented animal species. Ciprofloxacin treatment had no effect on the morphological structures of the retina and on electroretinographic findings.

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PART III: CONSUMER INFORMATION

Pr CIPROFLOXACIN
Ciprofloxacin Tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when CIPROFLOXACIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CIPROFLOXACIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
CIPROFLOXACIN is intended to treat infections in males or females over 18 years of age.
CIPROFLOXACIN should not be used to treat other infections.

What it does:
CIPROFLOXACIN is an antibiotic in the quinolone class that contain the active ingredient ciprofloxacin. CIPROFLOXACIN is formulated to be taken twice daily to kill bacteria causing infection. You should contact your doctor if your condition has not improved or if it has worsened while taking CIPROFLOXACIN.

When it should not be used:

- You should not take CIPROFLOXACIN if you are currently taking tizanidine (Zanaflex®) for the management of spasticity. Tizanidine concentrations may increase and cause further side effects such as drowsiness, sleepiness and low blood pressure.
- You should not take CIPROFLOXACIN if you have ever had a severe reaction to any of the ingredients contained within this medication or to the group of antibiotics known as "quinolones" (see What the non-medicinal ingredients are).

What the medicinal ingredient is:
Ciprofloxacin Hydrochloride USP

What the nonmedicinal ingredients are:
CIPROFLOXACIN tablets contain the following non-medicinal ingredients: colloidal silicon dioxide, corn starch crospovidone, magnesium stearate, microcrystalline cellulose, polyethyleneglycol, polyvinyl alcohol, pregelatinized starch, talc, titanium dioxide.

What dosage forms it comes in:
250 mg, 500 mg, and 750 mg tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use CIPROFLOXACIN talk to your doctor or pharmacist if any of the following apply to you:

- If you have a history of seizures;
- CIPROFLOXACIN is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPROFLOXACIN, talk to your doctor before taking this medication.
- CIPROFLOXACIN is not recommended for persons less than 18 years of age.

INTERACTIONS WITH THIS MEDICATION

It is important to let your health care professional know of all the medicines and supplements that you are using including the following:

- Theophylline or Videx®(didanosine) chewable/buffered tablets or pediatric powder
- Other medications including vitamin K antagonists like warfarin and acenocoumerol, glyburide, phenytoin, duloxetine, tizanidine, methylxanthines, caffeine, sevelamer, sucralfate, clozapine, ropinirole, lidocaine, sildenafil, pentoxifylline and certain heart medications known as antiarrhythmics which may interact with CIPROFLOXACIN
- antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron, or zinc all of which can interfere with the absorption of CIPROFLOXACIN and may prevent them from working. You should take CIPROFLOXACIN either 2 hours before or 6 hours after taking these products.
- Avoid excessive caffeine intake (e.g. coffee)

PROPER USE OF THIS MEDICATION

CIPROFLOXACIN should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however CIPROFLOXACIN may be taken with a meal that contains these products.

You should avoid excessive caffeine consumption while taking CIPROFLOXACIN.

Do not give it to other people even if they have a similar condition. If you have any concerns about your condition or your medicine, ask your doctor. Only your doctor can determine if CIPROFLOXACIN is right for you.

Usual dose:

CIPROFLOXACIN should be taken twice a day, twelve hours apart at approximately the same times each day with food or on an empty stomach.

Swallow the CIPROFLOXACIN tablets whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**

You should take CIPROFLOXACIN for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection.

Overdose:
Symptoms of ciprofloxacin overdose may include urination problems, joint pain, and muscle pain.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Should you forget to take it at the usual time, you may take your dose later in the day. Do not take more than two doses of CIPROFLOXACIN per day, even if you missed a dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

CIPROFLOXACIN is generally well tolerated. The most common side effects, which are usually mild, include nausea and diarrhea. Antibiotics of the quinolone class may also cause vomiting, rash, and abdominal pain/discomfort. If these symptoms persist, call your health care professional.

If you experience symptoms such as severe diarrhea (watery or bloody), fever, abdominal pain, you may have clostridium difficile colitis (bowel inflammation). If this happens, stop taking CIPROFLOXACIN and call your healthcare professional immediately.

You should be careful about driving or operating machinery until you are sure CIPROFLOXACIN is not causing dizziness.

Rare cases of allergic reactions have been reported in patients receiving quinolones, including ciprofloxacin, even after just one dose. If you develop hives, difficulty breathing, swelling of the tongue, throat, face, itching, serious skin reactions or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking CIPROFLOXACIN and call your health care professional.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPROFLOXACIN.

Quinolones, a class of antibiotics including CIPROFLOXACIN, have been rarely associated with inflammation of the tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking CIPROFLOXACIN, rest, avoid physical exercise and call your health care professional.

Treatment with a quinolone antibiotic, including CIPROFLOXACIN, may worsen muscle weakness in persons with myasthenia gravis. If you have myasthenia gravis, do not use CIPROFLOXACIN.

Neuropathy (problems in the nerves) has been reported in patients receiving quinolones, including CIPROFLOXACIN. If neuropathy symptoms occur such as pain, burning, tingling, numbness or weakness, you should stop taking CIPROFLOXACIN and contact your doctor immediately.

Seizures have been reported in patients receiving quinolone antibiotics including ciprofloxacin. If you have experienced seizures in the past, be sure to let your physician know that you have a history of seizures. Quinolones, including ciprofloxacin, have been rarely associated with other central nervous system events including confusion, tremors, headache, hallucinations, depression, agitation, insomnia, anxiety, nervousness and rarely, suicidal thoughts.

If you notice any side effects not mentioned in this section, or if you have concerns about side effects you may be experiencing, please inform your health care professional.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Stop taking drug and call your doctor or pharmacist
Uncommon	Body: • back, chest, pain, pain in extremities	✓
	Cardiovascular • rapid or irregular heart beat, inflamed veins • Hypotension • Chest pain, cardiac arrest (heart attack), cerebrovascular disorder, hot flashes, hyertension,	✓ ✓ ✓
	Digestive • Abdominal pain, anorexia, dry mouth, dyspepsia • enlarged abdomen, bowel inflammation, diarrhea (watery or bloody) • vomiting	✓ ✓ ✓
	Hypersensitiviy • Rash • Allergic reactions, hepatitis • Shock, pruritic rash, fever • Photosensitivity	✓ ✓ ✓ ✓
	Metabolic • Edema (face)	✓
	Musculoskeletal • Achiness, joint pain or swelling, tendon rupture, tendonitis, muscle pain.	✓
	Nervous System • Agitation, confusion, convulsion, dizziness, hallucinations, head ache, tremor • Paresthesia, depression, sleep disorder, migraine.	✓ ✓
	Other • Asthenia (general feeling of weakness)	✓
	Respiratory System • Shortness of breath	✓
	Special Senses • Abnormal vision, taste perversion	✓
	Urogenital system • Blood in urine	✓

This is not a complete list of side effects. For any unexpected effects while taking CIPROFLOXACIN*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store between 15°C and 30°C

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Cobalt Pharmaceuticals Company, at: 1-866-254-6111

This leaflet was prepared by Cobalt Pharmaceuticals Company.

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