PRODUCT MONOGRAPH

Pr CIPROFLOXACIN

Ciprofloxacin Hydrochloride Tablets
250 mg, 500 mg and 750 mg
Manufacturer's Standard

Antibacterial Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet: 250 mg, 500 mg, 750 mg	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Ciprofloxacin (ciprofloxacin hydrochloride) 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 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. A minimal inhibitory concentration (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*.

Empiric Therapy in Febrile Neutropenic Patients (in Combination with Piperacillin Sodium) (see DOSAGE AND ADMINISTRATION.)

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 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.

Geriatrics:
Elderly patients should receive a dose dependent on the severity of their illness and their creatinine clearance (see DOSAGE AND ADMINISTRATION: Special Populations: Impaired Renal Function for dose modification based on creatinine clearance or serum creatinine).

Pediatrics (<18 years of age):
The safety and efficacy of ciprofloxacin in individuals less than 18 years of age has not been established. Ciprofloxacin is not recommended for children under the age of 18 years (see WARNINGS AND PRECAUTIONS: Special Populations: Pediatrics (< 18 years of age)).

CONTRAINDICATIONS

- Ciprofloxacin (ciprofloxacin hydrochloride) is contraindicated in patients who have shown hypersensitivity to ciprofloxacin, or other quinolone antibacterial agents or any of the excipients. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.

- 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) (see DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions

- Ciprofloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients (see WARNINGS AND PRECAUTIONS: Cardiovascular).
- Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving quinolone therapy, including ciprofloxacin (see WARNINGS AND PRECAUTIONS: Immune).
- Fluoroquinolones including ciprofloxacin are associated with an increased risk of tendinitis and tendon rupture in all ages. The risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see WARNINGS AND PRECAUTIONS: Musculoskeletal).
- Fluroquinolones including ciprofloxacin may exacerbate muscle weakness in persons with myasthenia gravis. Avoid using ciprofloxacin in patients with a known history of myasthenia gravis (see WARNINGS AND PRECAUTIONS: Musculoskeletal).
- 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 should be used with caution in patients with known or suspected CNS disorders which may predispose them to seizures or lower the seizure threshold (see WARNINGS AND PRECAUTIONS: Neurologic).
- Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).

General

Prolonged use of ciprofloxacin 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.

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

Cardiovascular

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 (e.g., class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia) (see DRUG INTERACTIONS and ADVERSE REACTIONS).

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

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see ADVERSE REACTIONS).

There can be an increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin (see

ADVERSE REACTIONS).

Immune

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.

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

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. Cases of status epilepticus have also been reported. Ciprofloxacin may also cause central nervous system (CNS) stimulation which may lead to dizziness, tremors, restlessness, lightheadedness, confusion, hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and, rarely, suicidal thoughts or acts. In some cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behavior, such as attempted suicide or completed suicide. These reactions may occur even following the first dose of ciprofloxacin. If any of these reactions occur in patients receiving Ciprofloxacin 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 (e.g., severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction) (see ADVERSE REACTIONS).

Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and/or weakness have been reported in patients receiving quinolones, including ciprofloxacin.

Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition (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 should be used with caution and at a reduced dosage in patients with impaired renal function (see DOSAGE AND

ADMINISTRATION, DETAILED PHARMACOLOGY, Human Pharmacology).

Skin

Phototoxicity

Ciprofloxacin has been shown to produce photosensitivity reactions. 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 (e.g., sunburn-like skin reactions).

Vision Disorders

If vision disorder occurs in association with the use of ciprofloxacin, consult an eye specialist immediately.

Special Populations

Pregnant Women: The safety of ciprofloxacin in pregnancy has not yet been established. Ciprofloxacin should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus. Ciprofloxacin has been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing Women: The safety of ciprofloxacin in nursing women has not been established. 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.

Pediatrics (< 18 years of age): 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. 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. Ciprofloxacin is not recommended for use in pediatric patients and adolescents.

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

Monitoring and Laboratory 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

Adverse Drug Reaction Overview

The following sections summarize the safety information derived from clinical trials and postmarket use of ciprofloxacin.

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 is 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%.

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

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%).

Events possibly or probably drug-related occurring at a frequency of less than 1% with ciprofloxacin oral and IV 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 (at infusion site). 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, decreased appetite and food intake, 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 rarely: abnormal

prothrombin level, thrombocytopenia, thrombocytosis. The following have been reported very rarely: haemolytic anaemia, bone marrow depression (life-threatening), pancytopenia (life-threatening).

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, Immune). 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), toxic epidermal necrolysis (Lyell Syndrome, potentially life-threatening).

IV Infusion Site: thrombophlebitis, injection site reaction (e.g. edema / hypersensitivity / inflammation / pain). The following have been reported very rarely: burning, erythema, pain, paresthesia, and swelling.

Metabolic and Nutritional Disorder: creatinine increased. The following have been reported rarely: edema (face), hyperglycemia, hypoglycemia.

Musculoskeletal: The following have been reported rarely in patients of 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 myasthenia gravis) (see WARNINGS AND PRECAUTIONS, Musculoskeletal).

Nervous System: agitation, confusion, convulsion, dizziness, hallucinations, headache, hypesthesia, increased sweating, insomnia, somnolence, tremor (trembling). The following has been reported rarely: paresthesia (peripheral paralgesia), abnormal dreams (nightmares), anxiety, seizures (including status epilepticus), depression (potentially culminating in self-injurious behavior, such as suicidal ideations/thoughts and attempted or completed suicide) (see WARNINGS AND PRECAUTIONS, Neurologic). The following have been reported very rarely: apathy, ataxia, depersonalization, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, paresthesia, polyneuritis, sleep disorder, twitching, grand mal convulsions, abnormal (unsteady) gait, psychotic reactions (potentially culminating in self-injurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide), intracranial hypertension (including pseudotumor cerebri). 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, urticaria, rash, maculopapular rash. The following has been reported rarely: photosensitivity reaction, blistering. The following have been reported very rarely: alopecia, angioedema, fixed eruption, photosensitive dermatitis, petechia.

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.

Abnormal Hematologic and Clinical Chemistry Findings

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.

Adverse reactions noted during therapy with ciprofloxacin and metronidazole in clinical trials were similar to those already noted during therapy with ciprofloxacin alone with the following additions:

Cardiovascular: peripheral edema.

Digestive: colitis, gastritis, tongue discolouration.

Hemic and Lymphatic: coagulation disorder, thrombocythemia.

Skin: fungal dermatitis, pustular rash, sweating.

Metabolic: healing abnormal, hypernatremia.

Nervous: dementia.

Urinary: kidney tumour necrosis, urinary incontinence.

Post-Market Adverse Drug Reactions

The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and/or from worldwide post-marketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and in all indications): acute generalized exanthematous pustulosis (AGEP), 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).

The following has been reported at an unknown frequency: international normalized ratio (INR) increased (in patients treated with Vitamin K antagonists).

DRUG INTERACTIONS

Overview

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 reported in patients receiving theophylline alone; the possibility that ciprofloxacin may potentiate these reactions cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments should be made as appropriate.

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.

Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 1 - Established or Potential Drug-drug Interactions

Proper Name	Ref	Effect	Clinical Comment

Proper Name	Ref	Effect	Clinical Comment
Antidiabetic Agents	C	Disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, have been reported with quinolones, including ciprofloxacin, usually in diabetic patients receiving concomitant treatment with an oral antidiabetic agent (mainly sulfonylureas such as glyburide/glibenclamide, glimepiride) or with insulin.	In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient receiving ciprofloxacin, discontinue the drug immediately and an appropriate therapy should be instituted (see ADVERSE REACTIONS).
Caffeine and Other Xanthine Derivatives	CT	Caffeine has been shown to interfere with the metabolism and pharmacokinetics of ciprofloxacin. Excessive caffeine intake should be avoided. 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.	Caution and careful monitoring of patients on concomitant therapy of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products is recommended.
Class IA or III Antiarrhythmics	C	Ciprofloxacin may have an additive effect on the QT interval (see WARNINGS AND PRECAUTIONS).	Like other fluoroquinolones, precaution should be taken when using ciprofloxacin together with class IA (e.g., quinidine, procainamide) or III (e.g., amiodarone, sotalol) antiarrhythmics.
Clozapine	C	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).	Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin is advised.
Cyclosporine	CT	Some quinolones, including ciprofloxacin, have been associated with transient increases in serum creatinine levels in patients who are concomitantly receiving cyclosporine.	It is necessary to monitor the serum creatinine concentrations in these patients (twice a week).
Duloxetine	C	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.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Ferrous Sulfate	CT	Oral ferrous sulfate at therapeutic doses decreases the bioavailability of oral ciprofloxacin.	Ciprofloxacin should be administered at least 2 hours before or 6 hours after this preparation.
Calcium-Fortified Products (including Food and Dairy Products	CT	Although, ciprofloxacin may be taken with meals that include milk, simultaneous administration with dairy products alone, or with calcium-fortified products should be	It is recommended that ciprofloxacin be administered at least 2 hours before or 6 hours after substantial calcium intake

Proper Name	Ref	Effect	Clinical Comment
		avoided, since decreased absorption is possible.	(>800 mg) (see DOSAGE AND ADMINISTRATION).
Histamine H_2-receptor Antagonists	CT	Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.	No dosage adjustment is required.
Lidocaine	CT	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.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Methotrexate	C	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.	Patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.
Metoclopramide	CT	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.	No dosage adjustment is required.
Multivalent Cations	CT	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, 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. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products.	Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	CT	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.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Omeprazole	CT	Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of C_{max} and AUC of ciprofloxacin.	No dosage adjustment is needed.
Oral Anticoagulants	CT	Simultaneous administration of ciprofloxacin with an oral anticoagulant (e.g., vitamin K antagonist) may augment its anticoagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including quinolones. The risk may vary with the underlying infection, age, and general status of	INR and/or prothrombin time should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant (e.g., warfarin, acenocoumarol).

Proper Name	Ref	Effect	Clinical Comment
		the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess.	
Phenytoin	CT	Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously.	Monitoring of phenytoin therapy is recommended, including phenytoin serum concentration measurements, during and shortly after co-administration of ciprofloxacin with phenytoin to avoid the loss of seizure control associated with decreased phenytoin levels and to prevent phenytoin overdose-related undesirable effects.
Probenecid	CT	Probenecid blocks renal tubular secretion of ciprofloxacin and has been shown to produce an increase in the level of ciprofloxacin in the serum. 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.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Ropinirole	CT	In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a moderate 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.	Monitoring ropinirole-related undesirable effects, dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin
Sildenafil	CT	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.	Caution should be used when prescribing ciprofloxacin concomitantly with sildenafil, taking into consideration the risks and the benefits.
Theophylline	CT	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	CT	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).

Legend: C=Case Study; CT=Clinical Trial; T=Theoretical

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.

Drug-Food Interactions
Although ciprofloxacin may be taken with meals that include milk, simultaneous administration with dairy products alone (calcium intake > 800 mg), with calcium-fortified products, or mineral-fortified drinks, should be avoided since decreased absorption is possible. It is recommended that ciprofloxacin be administered at least 2 hours before or 6 hours after these preparations (see DRUG INTERACTIONS, Drug-Drug Interactions, and DOSAGE AND ADMINISTRATION, Dosing Considerations).

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
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.

Drug-Lifestyle Interactions
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.)

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.

Administration
Ciprofloxacin (ciprofloxacin hydrochloride) 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, 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 6 hours after substantial calcium intake (>800 mg) (see DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

Adults

The recommended dosages of oral Ciprofloxacin are:

Table 2: 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	1000 mg

* 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 q12h. Chronic bacterial prostatitis should be treated for 28 days with 500 mg q12h.

Definitive clinical studies have not been completed for severe infections other than in the respiratory tract.

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 3 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.

Special Populations

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 Phamacology). 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. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments.

Table 3: Maximum Daily Dose with Stated Creatinine Clearance or Serum Creatinine

Creatinine Clearance mL/min/1.73m^2	Maximum Daily Dose		Serum Creatinine Concentration mg/100 mL
	Oral	IV	
31-60	1000 mg	800 mg	1.4-1.9
≤30	500 mg	400 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 (< 10%) is removed from the body after hemodialysis or peritoneal dialysis. For hemodialysis patients, please follow dosing recommendations as described in Table 3. 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: $\frac{\text{Weight (kg) x (140 - age)}}{\text{49 x serum creatinine (mcmol/L)}}$

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 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, Special Populations, Pediatrics (<18 years of age)).

OVERDOSAGE

In the event of acute, excessive 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 Part II: SCIENTIFIC INFORMATION, MICROBIOLOGY). There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

Pharmacokinetics

(See DETAILED PHARMACOLOGY, Human Pharmacology)

General

Ciprofloxacin and metronidazole have been studied in combination and serum levels of ciprofloxacin are not significantly altered by metronidazole at the doses studied. Serum levels of metronidazole when administered orally at a dose of 500 mg q6h in combination with ciprofloxacin 500 mg PO q12h are: AUC_{0_6} 156.3 mg.h/L, C_{max} 31.3 mg/L and t_{max} 1.71 hours. Serum levels of metronidazole when administered intravenously at a dose of 500 mg IV q6h in combination with ciprofloxacin 400 mg IV q12h are: AUC_{0_6} 153.0 mg.h/L, C_{max} 33.6 mg/L and t_{max} 1.0 hours. (See DOSAGE AND ADMINISTRATION and DETAILED PHARMACOLOGY, Human Pharmacology.)

Following infusion of 400 mg IV Ciprofloxacin every eight hours in combination with 50 mg/kg IV piperacillin sodium every 4 hours, mean serum ciprofloxacin concentrations were 3.02 mcg/mL at 30 minutes and 1.18 mcg/mL between 6-8 hours after the end of infusion. The mean serum ciprofloxacin concentration given alone at 400 mg IV every eight hours was 3.67 mcg/mL at 30 minutes and 1.16 mcg/mL at 6 hours after the end of infusion.

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% to 80%. Maximum serum concentrations (C_{max}) and total areas under serum concentration vs. time curves (AUC) increased in proportion to dose.

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.

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a bid and tid IV dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute IV infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin both given every 12 hours produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg IV dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC

to 750 mg oral regimen given every 12 hours.

Distribution: The protein binding of ciprofloxacin is low (20% to 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 (M_1), sulphociprofloxacin (M_2), oxociprofloxacin (M_3) and formylciprofloxacin (M_4). M_1 to M_3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M_4, 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.

Special Populations and Conditions

Geriatrics: No dosage adjustment based on age alone is necessary for elderly patients. Compromised renal function may lead to increased drug exposure in this population group as ciprofloxacin is substantially excreted by the kidney (see DETAILED PHARMACOLOGY, Human Pharmacology).

Hepatic Impairment: 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).

Renal Impairment: Ciprofloxacin is eliminated primarily by renal excretion. Patients with renal insufficiency had significantly increased AUCs, prolonged (about 2-fold) elimination half-lives, and decreased renal clearances (see DETAILED PHARMACOLOGY, Human Pharmacology).

Some modification of dosage is recommended, particularly for patients with severe renal dysfunction. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION, Special Populations: Impaired Renal Function).

STORAGE AND STABILITY

Store between 15 and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Medicinal Ingredient: 250 mg, 500 mg, or 750 mg ciprofloxacin as ciprofloxacin hydrochloride. Nonmedicinal ingredients: microcrystalline cellulose, sodium starch glycolate, povidone, silica colloidal anhydrous, stearic acid, magnesium stearate, croscarmellose sodium, hypromellose, polyethyelene glycol, titanium oxide and talc.

Ciprofloxacin 250 mg tablet: White round film-coated tablet with breaking notch on one side. Embossed "cip" on top and "250" on the bottom of the breaking notch. Bottles of 100.

Ciprofloxacin 500 mg tablet: White oblong film-coated tablet with breaking notch on both sides. Embossed "cip" on one side of breaking notch and "500" on the other side, on one side of the tablet only. Bottles of 100.

Ciprofloxacin 750 mg tablet: White oblong film-coated tablet with breaking notch on both sides. Embossed "cip" on one side of breaking notch and "750" on the other side, on one side of the tablet only. Bottles of 50.

PART II: SCIENTIFIC INFORMATION

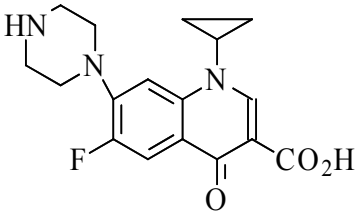
PHARMACEUTICAL INFORMATION

Drug substance

Proper Name: Ciprofloxacin hydrochloride

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

Structural Formula:



, HCl, H_2O

Molecular Formula: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

Molecular Mass: 385.8 g/mol

Physicochemical properties: Ciprofloxacin hydrochloride is a pale yellow crystalline powder. It is soluble in water. Its solubility in aqueous buffer of pH 7.4 at 21°C is 0.19 g/L, while the solubility is considerably higher at slightly acidic or slightly alkaline pH. At 140°C, water of crystallization is lost. At 307°C, decomposition takes place. The pH of ciprofloxacin hydrochloride is between 3 and 4.5 in a solution (1 in 40). The pK_{a1} is 6.5 and pK_{a2} is 8.9 determined using a $3x10^{-4}$M solution of 25°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single-centre, open, randomised, three period crossover study was performed to assess the bioequivalence of ciprofloxacin 1 x 500 mg tablets in healthy male subjects. The table below does not include data derived from the Swiss reference product Ciproxin®. The summary of the comparative bioavailability study is presented in the following table:

Summary Table of the Comparative Bioavailability Data From measured data (fasting conditions)

Parameter	Test** (A)	Reference† (B)	% Ratio of Geometric Means (A/B)	90% Confidence Interval
AUC_{0-t} (ng·h/mL)	7105 7398 (24.2)*	7471 7662 (21.7)*	95%	85-107
AUC_I (ng·h/mL)	7871 8154 (22.9)*	8237 8423 (20.5)*	96%	86-107
C_{max} (ng/mL)	2037 2114 (24.9)*	1999 2052 (21.1)*	102%	89-116
T_{max}* (h)	1.23 (42.8)	1.10 (40.2)	---	---
$T_{½}$* (h)	3.69 (9.0)	3.90 (14.6)	---	---
K_{el}* (h)	0.189 (9.6)	0.182 (14.7)	---	---

* expressed as arithmetic mean (CV %) only
†Ciprobay ® 500 mg tablet (Bayer German reference product).
** Ciprofloxacin 500 mg tablet (Sivem Pharmaceuticals ULC., Canada)

DETAILED PHARMACOLOGY

Animal Pharmacology

Effects on Histamine Release

Ciprofloxacin was administered intravenously to 9 anaesthetized dogs (initially with thiopental sodium at 25 mg/kg IV, followed by continuous infusion of a mixture of fentanyl 0.04 mg/kg/h and dehydrobenzperidol 0.25 mg/kg/h) 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.

Central Nervous System (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 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 4 and Figure 1).

Table 4: Pharmacokinetic Parameters Of Ciprofloxacin Following Single Doses In Healthy Volunteers Oral/IV

Dose	250 mg	500 mg	750 mg	200 mg IV*	400 mg IV*
C_{max} (mg/L)	1.42	2.60	3.41	2.14	4.60
$t_{½}$ (h)	4.19	4.87	5.34	3.4	3.5

Dose	250 mg	500 mg	750 mg	200 mg IV*	400 mg IV*
AUC $_{0-\infty}$ (mg•h/L)	5.43	10.60	15.03	5.24	11.69
t_{max} (h)	1.11	1.11	1.56	0.95	1.00

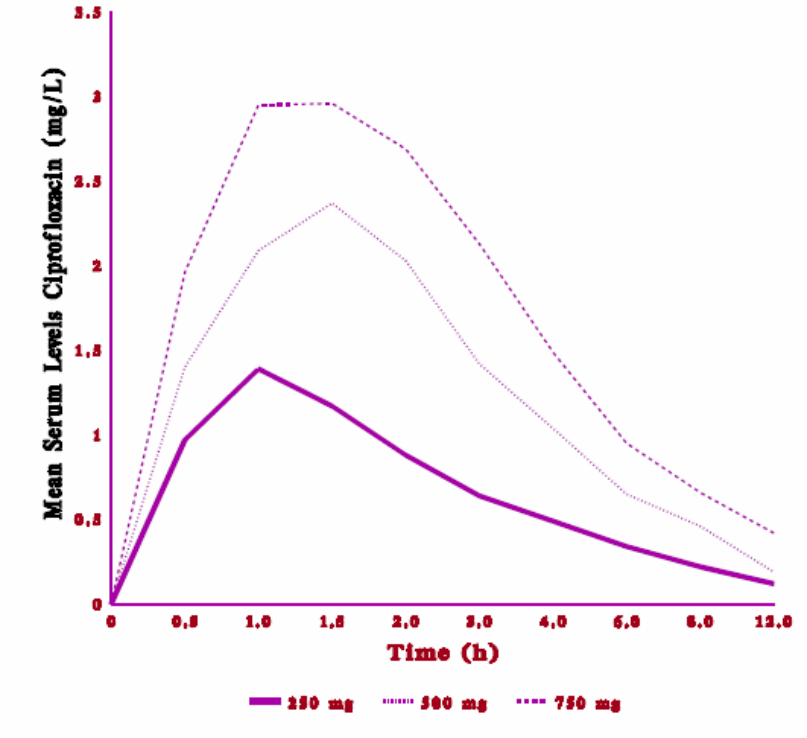
* IV parameters following a 60-minute infusion period

Similar values were obtained following the oral administration of multiple doses every 12 hours for 7 days (see Table 5).

Table 5: Mean Pharmacokinetic Parameters of Ciprofloxacin at Steady State in Healthy Volunteers

Regimen	AUC_{0-12h} (mg•h/L)	C_{max} (mg/L)	t_{max} (h)
(i) When administered alone			
Ciprofloxacin 500 mg PO q12h	13.7	2.97	1.23
Ciprofloxacin 400 mg IV q12h	12.7	4.56	1.0

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 6 shows urinary recovery data from another trial where healthy subjects were administered a single dose of ciprofloxacin in tablet form (see Table 6).

Table 6: Mean Urinary Excretion of Ciprofloxacin

Hours After Administration of a Single Dose				
	0 - 2	**2 - 4**	**4 - 8**	**8 - 12**
Urine Concentration mg/L (± 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)
200 mg IV	335.2 (±61.5)	99.9 (±16.0)	71.7 (±10.9)	31.24 (±4.06)
400 mg IV	706.0 (±99.0)	181.3 (±25.9)	127.1 (±18.9)	63.5 (±7.4)
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)
200 mg IV	58.8 (±9.3)	13.6 (±3.2)	14.1 (±9.0)	7.5 (±2.5)
400 mg IV	125.0 (±7.2)	24.1 (±4.7)	35.1 (±12.7)	15.7 3 (±.9)

Note: IV dose administered over 30 minutes.

Following the intravenous administration of a single 107 mg dose of ^{14}C-labelled ciprofloxacin to six healthy male volunteers (age: 23.7 ± 1.89 years, weight: 80.2 ± 3.45 kg), 15% of unchanged ciprofloxacin was recovered in the feces, suggesting that hepatic extraction and biliary excretion is an extra-renal clearance pathway for ciprofloxacin. Direct evidence of biliary excretion of ciprofloxacin was obtained in 12 patients (age 28-58) with T-tube drainage. A peak biliary concentration of 16 mg/L was seen 4 hours after a single oral dose of ciprofloxacin 500 mg.

After intravenous administration to a group of 9 healthy male volunteers (age: 26.8 ± 9.7 yrs, weight: 63.9 ± 6.4 kg), approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. After a 200 mg IV dose, urine concentrations of ciprofloxacin usually exceed 200 mcg/mL during the first two hours after dosing, and are generally greater than 10 mcg/mL at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing. Approximately 15% of an IV dose is recovered from the feces within 5 days after dosing, which may arise from either biliary clearance or transintestinal elimination. Following intravenous administration, approximately 10% of the dose is recovered in the urine in the form of metabolites.

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 IV.

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 7 summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

Table 7: 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 (h)
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
Bronchial Tissues	10	200 mg IV	3.94 ± 2.5	1.62 ± 0.7	0.97
Vagina	18	100 mg IV	1.13 ± 0.2	0.61 ± 0.12	0.5
Ovary	18	100 mg IV	1.00 ± 0.23	0.61 ±0.12	0.5

Special Populations

Geriatrics

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 8: 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
$t_{½}$ (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

Renal Impairment

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. 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 9) were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment (see Group II, Table 9) and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis (see Group III, Table 9). 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 9).

Table 9: 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 m²) (mL/min/1.73 m²)	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 injection 200 mg, there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

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 $1x\ 10^{-6}$.

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 inoculum 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 cloaceæ
Escherichia coli
Haemophilus influenzæ
Haemophilus parainfluenzæ
Klebsiella pneumoniæ
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeæ
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Serratia marcescens
Shigella boydii
Shigella disenteriæ
Shigella flexeneri
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 mcg/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 trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus
Staphylococcus hominis

Aerobic gram-negative microorganisms

Acetinobacter iwoffi
Aeromonas hydrophila
Edwardsiella tarda
Enterobacter ærogenes
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 Tests

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 10.

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 mcg 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 mcg ciprofloxacin disk should be interpreted according to the criteria outlined in Table 10. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

Table 10: Susceptibility Interpretative Criteria for Ciprofloxacin						
	MIC (mcg/L)			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 æruginosa	≤1	2	≥4	≥21	16-20	≤15
Hæmophilus influenzæ	≤1[a]	[g]	[g]	≥21[b]	[g]	[g]
Hæmophilus parainfluenzæ	≤1[a]	[g]	[g]	≥21[b]	[g]	[g]
Streptococcus pyogenes	≤1[c]	2[c]	≥4[c]	≥21[d]	16-20[d]	≤15[d]
Neisseria gonorrhoeæ	≤0.06 [e]	0.12-0.5[e]	≥1[e]	≥41[f]	28-40[f]	≤27[f]

Abbreviations: I= Intermediate; MIC= minimum inhibitory concentration; mcg=microgram; mL= milliliter;
mm=millimeter;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 11. For diffusion technique, the 5 mcg ciprofloxacin disk should provide the zone diameters outlined in Table11.

Table 11: Quality Control for Susceptibility Testing		
Strains	**MIC range (mcg/L)**	**Zone Diameter (mm)**
Enterococcus faecalis ATCC 29212	0.25- 2	-
Escherichia coli ATCC 25922	0.004- 0.015	30- 40

Table 11: Quality Control for Susceptibility Testing		
Strains	**MIC range (mcg/L)**	**Zone Diameter (mm)**
Hæmophilus influenzæ ATCC 49247	0.004- 0.03 [a]	34- 42 [d]
Pseudomonas æruginosa ATCC 27853	0.25 -1	25- 33
Staphylococcus aureus ATCC 29213	0.12- 0.5	-
Staphylococcus aureus ATCC 25923	-	22- 30
Neisseria gonorrhoeæ 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; mcg=microgram; mL= milliliter; mm=millimeter;
[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 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

Table 12: LD_{50} (mg/kg) across species

Species	Mode of Administration	LD_{50} mg/kg
Mouse	PO	Approx. 5000
Rat	PO	Approx. 5000
Rabbit	PO	Approx. 2500
Mouse	IV	Approx. 290
Rat	IV	Approx. 145
Rabbit	IV	Approx. 125
Dog	IV	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 due 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 V79 Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiæ: 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 Tolerability studies

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 occurred 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 tolerability 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

Ciprofloxacin
ciprofloxacin hydrochloride tablets

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 used to treat certain types of bacterial infections.

What it does:
Ciprofloxacin is a antibiotic that kills the bacteria causing the infection.

When it should not be used:
Do not use Ciprofloxacin if you:

- are allergic to ciprofloxacin, other quinolone antibiotics or to any nonmedicinal ingredients in these products (see What the nonmedicinal ingredients are).
- are currently taking tizanidine for the management of spasticity. Tizanidine concentrations may increase and cause further side effects such as drowsiness, sleepiness and low blood pressure.

What the medicinal ingredient is:
ciprofloxacin as ciprofloxacin hydrochloride.

What the nonmedicinal ingredients are:
croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethyelene glycol, povidone, silica colloidal anhydrous, sodium starch glycolate, stearic acid, talc, titanium oxide.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Ciprofloxacin has been shown to lengthen the heartbeat on an electrocardiogram test (QT interval prolongation).**
- **Serious hypersensitivity (allergic) reactions have been reported in some patients receiving quinolone therapy, including ciprofloxacin.**
- **If you have myasthenia gravis, treatment with Ciprofloxacin may make your condition worse. Do not use Ciprofloxacin if you have this condition.**
- **Quinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. Speak to your doctor to determine if this medication is suitable for you.**
- **Seizures and toxic psychoses may occur with quinolone therapy. Tell your doctor if you have any central nervous system problems (i.e., epilepsy). Your doctor will determine whether you should use this medication.**
- **Ciprofloxacin can cause liver injury which may be fatal.**

BEFORE you use Ciprofloxacin talk to your doctor or pharmacist if you:

- Have a history of seizures
- Have a heart condition known as "QT prolongation"
- Have low levels of potassium in your blood
- Have liver or kidney disease or damage
- Are pregnant, planning to become pregnant, breast feeding or planning to breast feed. Ciprofloxacin is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.
- Are less than 18 years of age.
- Have a history of tendon problems associated with the use of a quinolone antibiotic.
- Have a condition known as myasthenia gravis.

You may become sensitive to the sun and ultraviolet light while taking Ciprofloxacin. Exposure to sunlight and ultraviolet light, such as that used in tanning salons, should be minimized until you know how you respond.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to Ciprofloxacin as it can cause dizziness.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with Ciprofloxacin include:

- Theophylline or didanosine chewable/buffered tablets or pediatric powder. **Serious and fatal reactions have been reported in patients receiving ciprofloxacin and theophylline.**
- 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.
- Antidiabetic agents (eg, glyburide, glibenclamide, glimepiride, insulin) as the combination of any of these agents with ciprofloxacin may cause lower blood sugar.
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
- Caffeine (e.g. coffee) and other xanthine derivatives (e.g. pentoxifylline). Excessive caffeine intake should be avoided while taking Ciprofloxacin.
- Certain heart medications known as antiarrhythmics (eg, quinidine, procainamide, amiodarone, sotalol)
- Other medications including oral anticoagulants (like warfarin and acenocoumarol), phenytoin, duloxetine, tizanidine, methylxanthines, sevelamer, sucralfate, clozapine, ropinirole, lidocaine, sildenafil, probenecid, methotrexate, metoclopramide, cyclosporine, and lanthanum carbonate

PROPER USE OF THIS MEDICATION

- Ciprofloxacin should be taken as prescribed at approximately the same times each day with food or on an empty stomach.
- 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 (see Interactions With This Medication).
- You should avoid excessive caffeine consumption while taking Ciprofloxacin.
- You should drink lots of water while taking Ciprofloxacin
- Swallow the Ciprofloxacin tablets whole, with water if needed. **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

Remember:
- Take your dose of Ciprofloxacin as prescribed.
- Complete the course of Ciprofloxacin even if you are feeling better.
- Do not use Ciprofloxacin for another condition or give it to others.

This information does not take the place of discussions with your doctor or health care professional about your medication or treatment.

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

Side effects may include:
- Nausea and vomiting
- Diarrhea
- Rash, blistering of skin
- Stomach pain/discomfort, gas
- Cramping
- Coordination problems (unsteady walk)
- Dizziness, fainting
- Feeling unwell
- Increased muscle tone, inflammation of joints, muscle pain
- Loss of appetite
- Loss of hearing (tinnitus)
- Migraine
- Sleeping problems
- Problems with smell and taste
- Sweating
- Visual disturbances (eyesight problems)

If your eyesight worsens or changes in any way, consult your doctor and eye specialist immediately.
If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have Clostridium difficile colitis (bowel inflammation). If this occurs, stop taking Ciprofloxacin and contact your healthcare professional immediately.

If any of these affect you severely, tell your doctor or pharmacist.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Rare	**Allergic Reaction**: rash, hives (skin eruptions), swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, rapid heartbeat			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Central Nervous System Disorders: Seizures/ convulsions, confusion, tremors, hallucinations, depression, suicidal thoughts or psychotic reactions			✓
	Photo-sensitivity Reaction: Sensitivity to light, blistering of skin			✓
	Tendon pain, inflammation, or rupture			✓
	Increased Blood Sugar: Frequent urination, thirst, hunger, tiredness, blurred vision, headache, trouble concentrating	✓		
	Low Blood Sugar: dizziness, weakness, headache, sweating, hunger	✓		
Unknown	**Severe Bowel Disorder:** Persistent diarrhea, bloody or watery diarrhea, abdominal or stomach pain/cramping, blood/mucus in stool			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Nerve Disorder (Neuropathy): Pain, burning, tingling, numbness, weakness		✓	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, pale stools		✓	
	Heart Disorder (QT Prolongation): Irregular heartbeat		✓	

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 and 30°C.

Keep out of reach and sight 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, Ontario
    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 found by contacting the sponsor, Sivem Pharmaceuticals ULC, at:

1-855-788-3153

or www.sivem.ca

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