PRODUCT MONOGRAPH

MINT-Ciprofloxacin

Ciprofloxacin Tablets, USP

250 mg, 500 mg, 750 mg Ciprofloxacin as Ciprofloxacin Hydrochloride

Antibacterial Agent

Manufactured for:
Mint Pharmaceuticals Canada Inc.,
1 First Canadian Place, Suite 5600
100 King Street West
Toronto, Ontario
M5X 1E2

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THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTION AND CLINICAL PHARMACOLOGY

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 actions 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 **MICROBILOGY**) There is not cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

Clinical Pharmacology (See **HUMAN PHARMACOLOGY**)

Absorption

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

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

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 i.v. dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute i.v. 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 i.v. 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 (20-30%), and the substance is present in plasma largely in a non-ionized form. Ciprofloxacin can diffuse freely into the extravascular space. The large steady-state volume of distribution of 2-3 L/kg body weight shows that ciprofloxacin penetrates in tissues resulting in concentrations which clearly exceed the corresponding serum levels.

Metabolism

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

Elimination

MINT-Ciprofloxacin is largely excreted unchanged both renally and to a smaller extent non-renally. Renal clearance is between 0.18-0.3 L/h/kg and the total body clearance between 0.48-0.60 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 a metabolization. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

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 POq12h are: AUC_{0-6} 156.4 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.mg.h.L, C_{max} 33.6 mg/L and t_{max} 1.0 hours. (See **DOSAGE AND ADMINISTRATION AND HUMAN PHARMACOLOGY)**

Clinical Trials

A comparative, randomized, single dose, 2 way crossover bioavailability studies was performed under fasting conditions in healthy adult male volunteers. A summary of the pharmacokinetic parameters is given in the table below:

Ciprofloxacin (as ciprofloxacin hydrochloride) Tablets (1 x 750 mg tablet) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test MINT-Ciprofloxacin Tablets**	**Reference Cipro®†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.h/mL)	17363.71 17710.9 (20.6)	17384.02 17745.9 (21.4)	99.9	93.4 - 106.8
AUC_I(ng.h/mL)	17857.52 18200.4 (20.2)	17844.40 18221.9 (21.6)	100.1	93.6 - 107.0
C_{max} (ng/mL)	3247.9521 3303.478 (19.1)	3222.3760 3307.391 (24.5)	100.8	94.4 - 107.6
T_{max} (h)[$]	1.611 (39.6%)	1.774 (44.3%)		
$T_{1/2}$ (h) [$]	4.977 (14.7%)	4.668 (11.2%)		

†Cipro® is manufactured by Bayer Inc. and was purchased in Canada.

[$] Expressed as arithmetic (CV %) only.

INDICATIONS AND CLINICAL USES

Oral Administration

MINT-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
Streptococcus pneumoniae

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

Acute sinusitis caused by:
Haemophilus influenzae
Moraxella catarrhalis
Streptococcus pneumoniae

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, MINT-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. An MIC determination on the isolate from the index case should be performed as soon as possible. **Ciprofloxacin is not indicated for the treatment of meningococcal meningitis.**

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

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

CONTRAINDICATIONS

MINT-Ciprofloxacin (ciprofloxacin hydrochloride) is contraindicated in patients who have shown hypersensitivity to ciprofloxacin or other quinolone antibacterial agents or any of the excipient.

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

WARNINGS

The safety of MINT-Ciprofloxacin (ciprofloxacin hydrochloride) in pediatric patients and adolescents (under the age of 18 years), pregnant women and nursing women has not yet been established. (See **PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Women**)

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.

CNS and Psychiatric Effects

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and rarely, suicidal thought or acts. In rare cases, depression or psychosis can progress to self-endangering behaviour. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As will all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors predispose to seizures and lower the seizure threshold. (See **ADVERSE REACTIONS)**

Cytochrome P450

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

Hypersensitivity

Serious hypersensitivity and/or anaphylactic reactions have been reported in patient receiving quinolone therapy, including ciprofloxacin. 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 sever 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.

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with virtually all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients with diarrhoea subsequent to the administration of antibacterial agents. Subsequent to diagnosis of pseudomembranous colitis, therapeutic measures should be initiated. Mild cases with usually respond to discontinuation of drug alone. In moderate to severe cases, consideration should be given to the management with fluids, electrolytes, protein supplementation and treatment with antibacterial drug effective against *C. difficile.*

PRECAUTIONS

Tendon rupture (predominantly achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids. At any sign of tendonitis (i.e., painful swelling), the administration of ciprofloxacin should be discontinued, physical exercise avoided, and a physician consulted.

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.

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

Prolonged use of MINT-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.

Pregnancy

The safety of MINT-Ciprofloxacin in pregnancy have not yet been established. MINT-Ciprofloxacin should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus. (See **WARNINGS**) MINT-Ciprofloxacin have been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing Women

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from women taking ciprofloxacin a decision should be made to discontinue

nursing or to discontinue the administration MINT-Ciprofloxacin, taking into account the importance of the drug to the mother and the possible risk to the infant (see **WARNINGS**)

Pediatric Use

The safety and efficacy of ciprofloxacin in the pediatric population less than 18 years of age have not been established. Quinolones, including ciprofloxacin, causes anthropathy and osteochondrosis in juvenile animals of several species (See **WARNINGS, TOXICOLOGY**).

Elderly

Ciprofloxacin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patient with impaired renal function. (See **HUMAN PHARMACOLOGY**)

Renal Impairment

Since ciprofloxacin is eliminated primarily by the kidney, MINT-Ciprofloxacin should be used with caution and at a reduced dosage in patients with impaired renal function. (See **DOSAGE AND ADMINISTRATION, 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 **HUMAN PHARMACOLOGY**).

Ability to Drive and Operate Machinery

Even when ciprofloxacin is taken exactly as prescribed, it can affect the speed of reaction to such an extent that the ability to drive or to operate machinery is impaired. This applies particularly in combination with alcohol.

Drug Interactions

Concurrent administration of ciprofloxacin with theophylline may lead to an elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (see **ADVERSE REACTIONS**) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

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

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

Quinolones have been reported to increase the effects of the oral anticoagulant warfarin and its derivatives. During concomitant administration of these drugs, the prothrombin time or other appropriate coagulation tests should be closely monitored.

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

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.

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation containing products such as magnesium/aluminum antacids, polymeric phosphate binders such as sevelamer, sucralfate, Videx® (didanosine) chewable/buffered tablet 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 considerable lower than

desired. Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.

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 of 2 hours after substantial calcium intake (>800 mg). (See **DOSAGE AND ADMINISTRATION)**

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

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

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

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

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.

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 **CONTRADICATIONS, WARNINGS**)

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.

ADVERSE REACTIONS

MINT-Ciprofloxacin (ciprofloxacin hydrochloride) is generally well tolerated. During worldwide clinical investigation, 16,580 courses of ciprofloxacin treatment were evaluated for drug safety.

Adverse events, possibly, probably or highly probably related to ciprofloxacin occurred in 1395 (8.8%) of patients. The adverse reactions according to treatment (oral) show that the incidence of adverse reactions was 8.0% for the group treated orally, 17% for the group treated with ciprofloxacin I.V. and 15.3% for the group treated sequentially. The difference between the oral and i.v. group relates to adverse vascular reactions which are known to be associated with i.v. administration.

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, probably drug-related occurring at a frequency of less than 1% with ciprofloxacin oral 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. The following have been reported rarely ≥0.01% <0.1%): hypotension, The following have been reported very rarely (<0.01%): angina pectoris, atrial fibrillation, cardiac arrest, cerebrovascular disorder, electrocardiogram abnormality, hot flashes, hypertension, kidney vasculitis, myocardial infarct, pericarditis, pulmonary embolus, substernal chest pain, syncope (fainting), vasodilation (hot flashes).

Digestive: abdominal pain, anorexia, dry mouth, dyspepsia, dysphagia, enlarged abdomen, flatulence, gastrointestinal moniliasis, jaundice, stomatitis, vomiting, abnormal liver function test. The following have been reported rarely: moniliasis (oral), cholestatic jaundice and pseudomembranous colitis. The following have been reported very rarely: constipation, esophagitis, gastrointestinal haemorrhage, glossitis, hepatomegaly, ileus, increased appetite, intestinal perforation, life-threatening pseudomembranous colitis with possible fatal outcome, liver damage, melena, pancreatitis, tenesmus, tooth discoloration, toxic megacolon, ulcerative stomatitis.

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

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

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

Musculoskeletal: The following have been reported rarely: achiness, arthralgia (joint pain), joint disorder (joint swelling), pain in the extremities, partial or complete tendon rupture (predominantly achilles tendon), tendonitis (predominantly achillotendonitis), myalgia (muscular pain). The following have been reported very rarely: myasthenia (exacerbation of symptoms of myasthensia gravis).

There have been 54 reports of arthropathies with ciprofloxacin. Ten of these reports involved children. Arthralgia was usually the first symptom which led to rapid assessment and withdrawal of the drug. No irreversible arthropathies have been observed.

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

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

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

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

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

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

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

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

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 discoloration

Hemic and Lymphatic: coagulation disorder, thrombocythemia

Skin: fungal dermatitis, pustular rash, sweating

Metabolic: healing abnormal, hypernatremia,

Nervous: dementia

Urinary: kidney tumour necrosis, urinary incontinence.

The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide post-marketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and in all indications): arrhythmia, atrial flutter, bleeding diathesis, bronchospasm, *C. difficile* associated diarrhea, candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular, collapse, cerebral thrombosis, chills, delirium, drowsiness, dysphasia, edema (conjunctivae, hands, lips, lower extremities, neck), epistaxis, exfoliative dermatitis, fever, gastrointestinal bleeding, gout (flare up), gynecomastia, hearing loss, hemoptysis, hemorrhagic cystitis, hyperpigmentation, joint stiffness, lightheadedness, lymphadenopathy, manic reaction, myoclonus, nystagmus, pain (arm, breast, epigastric, foot, jaw, neck, oral mucosa), paranoia, phobia, pleural effusion, polyuria, postural hypotension, pulmonary embolism, purpura, QT prolongation (frequency < 1 per million), renal calculi, respiratory arrest, respiratory distress, restlessness, rhabdomyolysis, torsades de pointes (frequency < 1 per million), toxic psychosis, unresponsiveness, urethral bleeding, urination (frequent), ventricular ectopy, ventricular fibrillation (frequency < 1 per million), ventricular tachycardia (frequency < 1 per million), vesicles, visual acuity (decreased) and visual disturbances (flashing lights, change in colour perception, overbrightness of lights).

SYMPTOMS AND TREATMENT OF OVERDOSE

In the event of acute, excessive oral overdosage, reversible renal toxicity, arthralgia, myalgia and CNS symptoms have been reported. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer magnesium- or calcium-containing antacids which reduce the absorption of ciprofloxacin and to maintain adequate hydration.

Based on information obtained from subjects with chronic renal failure, only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

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.

Oral Administration

MINT-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 not take antacids containing magnesium or aluminum.

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

Although MINT-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 MINT-Ciprofloxacin be administered at least 2 hours before or 2 hours after substantial calcium intake. (>800 mg). (See **PRECUATIONS, Drug Interactions**)

Adults

The recommended dosages of MINT-Ciprofloxacin are:

Table 1: Recommended Dosages for Oral Ciprofloxacin

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Mild/Moderate	250 mg	q 12h	500 mg
	Severe/Complicated	500 mg	q 12h	1000 mg
Chronic Bacterial Prostatitis	Asymptomatic/Mild/ Moderate	500 mg	q 12h	1000 mg
Respiratory Tract Bone & Joint Skin & Soft Tissue	Mild/Moderate	500 mg	q 12h	1000 mg
	Severe*/Complicated	750 mg	q 12h	1500 mg
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q 12h	1000 mg
Urogenital and Extragenital Gonorrhea	Uncomplicated	500 mg	once	500 mg
Typhoid Fever	Mild/Moderate	500 mg	q 12h	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 q 12h. Chronic bacterial prostatitis should be treated for 28 days with 500 mg q 12h.

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine (see **HUMAN PHARMACOLOGY**). This alternate pathway of drug elimination appears to

compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides a guideline for dosage adjustment. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments.

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

Creatinine Clearance mL/min/1.73m^2	Maximum Daily Dose		Serum Creatinine Concentration mg/100mL
	Oral	I.V.	
31-60	1000 mg	800 mg	1.4-1.9
≤30	500 mg	400 mg	≥2.0

Maximum daily dose, 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 2. On dialysis days, the dose should be administered after dialysis.

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

Creatinine Clearance mL/sec =

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

Females: 0.85 x the above value

In traditional units mL/min =

Males: $\frac{\text{Weight (kg) x (140 - age)}}{\ldots}$

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**)

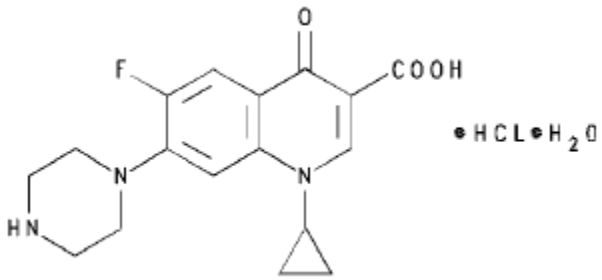
PHARMACEUTICAL INFORMATION

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:



Molecular Formula: $C_{17}H_{18}FN_3O_3$ HC1 H_2O

Molecular Weight: 385.8

Description: Ciprofloxacin hydrochloride is a pale yellow crystalline powder. It is sparingly 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 3 x 10^{-4} M solution of 25°C.

COMPOSITION

Tablets

Ciprofloxacin Hydrochloride
Microcrystalline Cellulose
Starch (corn)
Sodium Starch Glycolate
Colloidal Silicon Dioxide
Talc
Magnesium Stearate
Hypromellose
Titanium Dioxide
Polyethylene Glycol

STABILITY AND STORAGE RECOMMENDATIONS

Tablets: Store at room temperature 15°- 30°C.

AVAILABILITY OF DOSAGE FORMS

MINT-Ciprofloxacin 250 mg Tablets: White to off-white, round, film-coated tablets, debossed with “RX709" on one side and plain on the other side. Bottles of 100s.

MINT-Ciprofloxacin 500 mg Tablets: White to off-white, caplet shaped, film-coated tablets, debossed with “RX710" on one side and plain on the other side. Bottles of 100s.

MINT-Ciprofloxacin 750 mg Tablets: White to off-white, caplet shaped, film-coated tablets, debossed with “RX711" on one side and plain on the other side. Bottles of 100s.

MICROBIOLOGY

The *in vitro* activity of ciprofloxacin against clinical isolates of gram-positive and gram-negative aerobic and anaerobic bacteria is shown in Table 3. 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. Susceptibility was determined by agar and broth dilution tests, pH 7.1-7.4, using inoculum sizes ranging from 10^4 to 10^5 colony forming units per mL.

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. There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

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

Table 3: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin

		mg/L												
Genera or Species	**(Number of Strains)**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Acinetobacter antiratus	-42		2	12	19	52	86	95		98	100			
Actinomyces spp.	-3						33.3				100			
Branhamella catarrhalis	-28	4	43	100										
Campylobacter jejuni	-100			64	95	97	100							
Chlamydia trachomatis	-10							70	100					
Clostridium spp.	-8				10.0	55.0	75.0		95.0	100				
Clostridium perfringens	-12				8.3	83.3	100							
Citrobacter freundii	-19	88	94				100							
Citrobacter diversus	-3	66	100											
Citrobacter spp.	-4	100												
Enterobacter aerogenes	-5	50	83		100									
Enterobacter agglomerans	-2	100												
Enterobacter cloaceae	-49	61	86	96	100									
Escherichia coli	-203	84	92	93	96	98	99	100						
Flavobacterium brevie	-3						66	100						
Fusobacterium spp.	-8					25.0	50.0		75.0	87.5	100			
Haemophilus ducreyi	-72	100												
Haemophilus influenzae beta-lactamase positive	-50		90	100										
Klebsiella oxytoca	-32	78	97		100									
Klebsiella pneumonia	-40	21	72	85	90	97	100							

Table 3: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin

		mg/L												
Genera or Species	**(Number of Strains)**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Klebsiella species	-24	33	88	92		96	100							
Morganella morganii	-12	92	100											
Moraxella spp.	-5		20		40	60	80	100						
Neisseria gonorrhoeae beta-lactamase negative	-15		13	73	87	100								
Propionibacterium spp.	-42				2.4	28.6	88.1	92.9	100					
Proteus mirabilis	-57	28	88	93	98	100								
Proteus vulgaris	-3	100												
Providencia alcalifaciens	-6	33					66		100					
Providencia rettgeri	-5		80		100									
Providencia stuartii	-16	6	25	38	50	56	75		100					
Pseudomonas aeruginosa	-187	1	2	7	41	65	83	89	96		98	100		
Pseudomonas aeruginosa (Fibrocystic mucoid strain)	-(30)		3	20	43	63	80	100						
Pseudomonas aeruginosa (Fibrocystic non-mucoid strain)				13	50	93	100							
Pseudomonas aeruginosa (Bacteremic non-cystic strain)			3	57	88	100								
Pseudomonas cepacia	-10							50	100					
Pseudomonas fluorescens	-8				50	75	100							
Pseudomonas maltophilia	-11			9			36	55	64	82	91	100		
Salmonella spp.	-81		33	68	96	100								

Table 3: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin

		mg/L											
Genera or Species	**(Number of Strains)**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Serratia marcescens	-12		50	100										
Shigella spp.	-59		97	98	98	100								
Shigella sonnei	-45	100												
Staphylococcus aureus	-101		2	5	15	52	95	100						
Staphylococcus epidermidis	-64	5		6	28	84	95	100						
Streptococcus faecalis	-39						31	87	100					
Streptococcus pneumoniae	-51					9	27	100						
Ureaplasma urealyticum	-10						20	50	100					

The minimum inhibitory concentrations (MICs) of ciprofloxacin against aerobic bacteria are not significantly affected by changes in inoculum size in the range of 5 X 10^3 to 5 X 10^6 cfu/spot. Five bacterial species, *Staphylococcus aureus K734, Staphylococcus epidermidis H846, Streptococcus faecalis 7149, Escherichia coli 2345, and Proteus mirabilis 2349* were tested for MICs with inoculum size of 5 X 10^3 to 5 X 10^6. *Streptococcus faecalis* showed a four-fold increase while the remainder showed only a two to three-fold increase (Table 4). There were no differences between MICs determined in Mueller Hinton and Isosensitest broth.

MIC values 8 to 16 fold higher were seen when these organisms were tested in Mueller Hinton broth at pH 4.8 compared to values obtained at pH 7.3 (Table 4). This reduction in antibacterial activity suggests a significant pH effect.

Some studies have demonstrated that increasing the concentration of magnesium in the medium used for *in vitro* testing reduces the antibacterial activity of ciprofloxacin. Neither zinc nor calcium supplementation had the same effect. The mechanism by which magnesium antagonizes the activity of ciprofloxacin is unclear.

Table 4: Effect of Culture Medium Composition, pH and Inoculum Size On Antibacterial Activity of Ciprofloxacin

Organism/Strain		MIC (mg/L)				
		pH[(a)]			Inoculum Size (cfu)[(b)]	
		4.8	**7.3**	**8.8**	**5 x 10^3**	**5 x 10^6**
Staphylococcus aureus	K 734	4.0	0.5	0.5	0.25	0.5
Staphylococcus epidermidis	H 846	2.0	0.25	0.25	0.125	0.25
Streptococcus faecalis	7149	8.0	1.0	1.0	0.5	2.0
Escherchia coli	2345	0.5	0.016	0.016	0.008	0.016
Proteus mirabilis	2349	1.0	0.03	0.016	0.008	0.03

(a) Mueller Hinton broth (BBL) 5 x 10^5 cfu/mL.

(b) No difference between the MIC's determined in Mueller Hinton (BBL) and Isosensitest broth Oxiod).

Development of Resistance

Resistance to ciprofloxacin *in vitro* develops slowly via multiple-step mutation. Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $<1x10^{-9}$ to 1×10^{-6}. The prevalence of resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections.

Susceptibility Testing

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*, *Enterococcus species*, and *Staphylococcus* species.

MIC (μg/mL)	Interpretation	
≤ 1	Susceptible	(S)
2	Intermediate	(I)
≥ 4	Resistant	(R)

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. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory

procedures. Standard ciprofloxacin powder should provide the following MIC values:

Microorganism		**Zone Diameter(mm)**
Enterococcus faecalis	ATCC 29212	0.25 – 2.0
Escherichia. coli	ATCC 25922	0.004 - 0.015
Staphylococcus aureus	ATCC 25923	0.12 - 0.5

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 requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 µg ciprofloxacin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	**Interpretation**
≥ 21	Susceptible (S)
16 - 20	Intermediate (I)
≤ 15	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 µg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Table 5: Daily Ranges for Ciprofloxacin for Quality Control Samples

QC Strains	**Disk Zone Diameter (mm)**	**MIC (mg/L)**
S. aureus (ATCC 25923)	22 - 30	-
S. aureus (ATCC 29213)	-	0.25 - 1.0
E. coli (ATCC 25922)	30 - 40	0.008 - 0.03
P. aeruginosa (ATCC 27853)	25 - 33	0.25 - 1.0
*N. gonorrhoeae (*ATCC49226)	48 - 58	≤0.008

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Effects on histamine release

Ciprofloxacin was administered intravenously to 9 anaesthetized dogs (initially with thiopental sodium at 25 mg/kg i.v., followed by continuous infusion of a mixture of fentanyl 0.04 mg/kg/hr and dehydrobenzperidol 0.25 mg/kg/hr) at a single dose of 3, 10 or 30 mg/kg. Ciprofloxacin treatment resulted in circulatory changes similar to those caused by histamine release. These were reductions in blood pressure, cardiac output and maximum rate of pressure increase in the left ventricle (dp/dt max), and increase in heart rate. This histamine-liberating effect was counteracted by the simultaneous intravenous administration of 0.01 mg/kg pyrilamine maleate. No signs of histamine liberation were observed on conscious animals.

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

Bronchodilatory Effects

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

CNS Effects

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

Gastrointestinal Effects

Ciprofloxacin was administered orally to 4 groups of 20 mice each at doses of 0, 10, 30, and 100 mg/kg, 40 minutes prior to a 15% charcoal suspension. No effect was observed in intestinal

charcoal transit time. When given to 3 groups of 20 rats each at doses of 0, 30 or 100 mg/kg, no gastric lesions were observed on sacrificing the animals after 5 hours.

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

Effect on Blood Glucose and Serum Triglycerides

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

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

HUMAN PHARMACOLOGY

Pharmacokinetics

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

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin 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 6)

Pharmacokinetics were dose proportioned with no significant changes in clearance or half-life occurring over this dose range (see below)

Table 6: Pharmacokinetic Parameters Of Ciprofloxacin Following Single Doses In Healthy Volunteers Oral

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

Similar values were obtained following the oral administration of multiple doses every 12 hours for 7 days.

Table7: Mean Pharmacokinetic Parameters of Ciprofloxacin and Metronidazole at Steady State in Healthy Volunteers

Regimen	**AUC (mg.h/L)**	**C_{MAX} (mg/L)**	**T_{MAX} (h)**
(i)When administered alone			
Ciprofloxacin 500 mg PO q12h	13.7 (AUC_{0-12})	2.97	1.23
(ii)When administered as Ciprofloxacin 500 mg PO q12h in combination with Metronidazole 500 mg PO q6h			
Ciprofloxacin	12.6 (AUC_{0-12})	2.73	1.3
Metronidazole	156.3 (AUC_{0-6})	31.3	1.71

Figure 1

Mean Ciprofloxacin Serum Concentration After Single Oral Doses

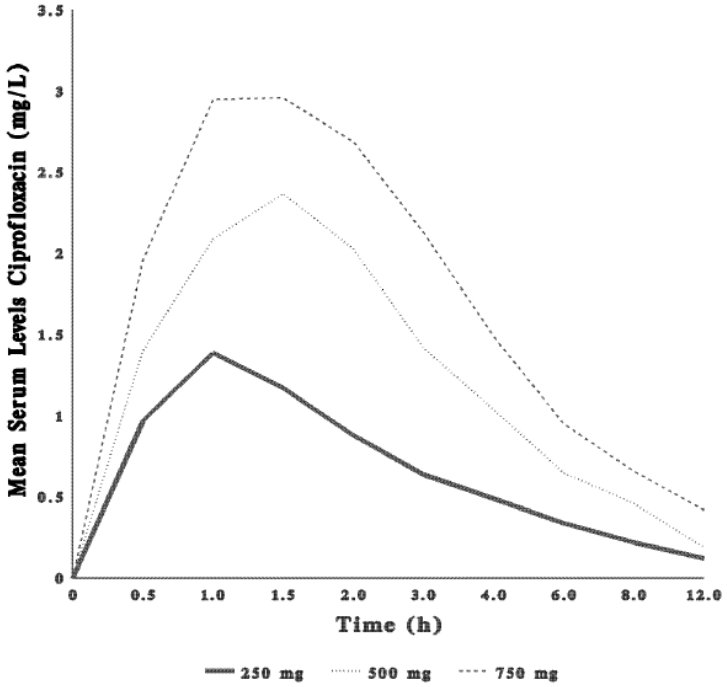


Table 8: Mean Urinary Excretion of Ciprofloxacin

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)
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)

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%.

FACTORS INFLUENCING THE PHARMACOKINETICS

Age (Elderly)

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

concentrations, overall elimination half-life and urinary recovery of ciprofloxacin were similar in both age groups.

Table 9: Comparison of pharmacokinetic parameters between healthy elderly and healthy younger volunteers

Parameter	Elderly Volunteers (mean ± S.D.)	Younger Volunteers (mean ± S.D.)
C_{max} (mg/L)	1.8 ± 0.5	1.3 ± 0.4
Tmax (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

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patient 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 10) were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment (see Group II, Table 10) and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis (see Group III, Table 10). 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 10).

Table 10: Mean Pharmacokinetic Parameters for Ciprofloxacin Following a Single 250 mg Oral Dose 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 I.V. 200 mg there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

Food

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

Drug Interactions

Theophylline

Studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline, resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions.

Caffeine

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

Multivalent Cations

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

Probenecid

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

Serum Protein Binding

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

Tissue Concentrations

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

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

Table 11 summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

Table 11: Distribution of Ciprofloxacin in Human Tissue/Fluid

Tissue/Fluid	No. of Patients	Single Dose of Ciprofloxacin	Peak Concentration (mg/kg or mg/L)		Mean Serum Concentration (mg/L)		Time After Dose (hr)
Skin Blister Fluid	6	500 mg po	1.4	± 0.36	2.3	± 0.7	1 - 6
Bone	4	750 mg po	1.4	± 1.0	2.9	± 2.2	2 - 4
Gynecological Tissue	18	500 mg po	1.3 to 1.6	± 0.66 ± 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

TOXICOLOGY

Acute Toxicity

Species	Mode of administration	LD50 (mg/kg)
Mouse	p.o.	approx 5000
Rat	p.o	approx 5000
Rabbit	p.o.	approx 2500
Mouse	i.v.	approx 290
Rat	i.v.	approx 145
Rabbit	i.v.	approx 125
Dog	i.v.	approx 250

Chronic Toxicity

Subacute Tolerability Studies over 4 weeks

Oral administrations**:** Doses up to and including 100 mg/kg were tolerated without damaged 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 administrations: 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 there 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 haemoglobin 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: Microsomes Test (Negative)
E. coli: DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo cell Transformation Assay (Negative)
Saccharomyces cerevisiae: Point Mutation Assay (Negative)
Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte Primary Culture DNA Repair Assay (LIDS) (Positive)

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

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)
Chinese Hamster Bone Marrow

Special Tolerability Studies

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

Renal Tolerability: 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 doe 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 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 cause damage to the large, weight-bearing 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 has no effect on the morphological structures of the retina and on electroretinographic findings.

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