PRODUCT MONOGRAPH

Pr CIPROFLOXACIN INJECTION

10 mg/mL ciprofloxacin

as ciprofloxacin lactate in Water for Injection

USP

Antibacterial Agent

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THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTION AND CLINICAL PHARMACOLOGY

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

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

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

CLINICAL PHARMACOLOGY (See HUMAN PHARMACOLOGY)

Absorption

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 formylciprofloxacin (M4). M1 to M3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M4, with the smallest quantity, is largely equivalent to norfloxacin in its antimicrobial activity.

Elimination

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 as metabolization. One percent (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 intravenously at a dose of 500 mg i.v. q6h in combination with ciprofloxacin 400 mg i.v. q12h are: $AUC_{0\rightarrow6}$ 153.0 mg·h/L, C_{max} 33.6 mg/L, and t_{max} 1.0 hour. (See **DOSAGE AND ADMINISTRATION** and **HUMAN PHARMACOLOGY**.)

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

INDICATIONS AND CLINICAL USES

Intravenous Administration

Ciprofloxacin Injection may be indicated for the treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

Respiratory Tract Infections

Acute pneumonia caused by:

Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, 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, Ciprofloxacin Injection 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 complicated urinary tract infections including pyelonephritis caused by:

Citrobacter diversus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa

Skin or Skin Structure Infections

Caused by:

Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes.

Septicemia

Caused by:

Escherichia coli, Salmonella typhi.

Bone

Caused by:

Enterobacter cloacae, Pseudomonas aeruginosa.

Complicated Intra-abdominal infections only when used in combination with metronidazole (See **DOSAGE AND ADMINISTRATION**)

Caused by:

Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Bacteroides fragilis.

Note: Most anaerobic bacteria, including *Bacteroides fragilis*, are resistant to ciprofloxacin. Therefore, ciprofloxacin should not be used as single agent therapy for complicated intra-abdominal infections. Efficacy against *Enterococcus* sp. in clinical trials has been shown to be only 75%.

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 Injection may be initiated before results of these tests are known. However, modification of this treatment may be required once results become available or if there is no clinical improvement. Culture and susceptibility testing performed periodically during therapy will provide information on the possible emergence of bacterial resistance. If anaerobic organisms are suspected to be contributing to the infection, appropriate therapy should be administered.

CONTRAINDICATIONS

Ciprofloxacin Injection is contraindicated in patients who have shown hypersensitivity to ciprofloxacin or other quinolone antibacterial agents.

WARNINGS

The safety of Ciprofloxacin Injection 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. Quinolones may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and rarely, suicidal thoughts or acts. 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 with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures or lower the seizure threshold. (See **ADVERSE REACTIONS**.)

Hypersensitivity

Serious hypersensitivity and/or anaphylactic reactions have been reported in patients 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 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.

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 diarrhea subsequent to the administration of antibacterial agents. Subsequent to diagnosis of pseudomembranous colitis, therapeutic measures should be initiated. Mild cases will 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 an antibacterial drug effective against *C. difficile*.

PRECAUTIONS

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

These reactions include cardiac arrest, seizure, status epilepticus and respiratory failure. Similar serious adverse events have been noted with administration of theophylline alone, however, the possibility that ciprofloxacin may potentiate these reactions cannot be eliminated. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

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 (i.e., sunburn-like skin reactions) occurs.

Intravenous infusion should be administered by slow infusion over a period of 60 minutes. Local i.v. reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less, or if small veins of the hand are used.

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

Nursing Women

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from women taking ciprofloxacin, a decision should be made to discontinue nursing or to discontinue the administration of Ciprofloxacin Injection, 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, cause arthropathy 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 patients with impaired renal function. (See **HUMAN PHARMACOLOGY**.)

Renal Impairment

Since ciprofloxacin is eliminated primarily by the kidney, Ciprofloxacin Injection 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.**)

Drug Interactions

Concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See **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, sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. Ciprofloxacin should be administered at least 2 hours before or 6 hours after intake of antacids containing magnesium or aluminum, sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc.

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

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, patients under methotrexate therapy should be carefully monitored when 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.

ADVERSE REACTIONS

Ciprofloxacin Injection is generally well tolerated. During worldwide clinical investigation, 16,580 courses of ciprofloxacin treatment from all dosage forms were evaluated for drug safety.

Adverse events, possibly, probably or highly probably related to ciprofloxacin occurred in 1,395 (8.8%) of patients receiving oral or i.v. dosage forms. The adverse reactions according to treatment show that the incidence of adverse reactions was 17% for the group treated with Ciprofloxacin Injection. A higher incidence in the i.v. group in comparison to the oral relates to adverse vascular reactions which are known to be associated with i.v. administration.

In patients treated with Ciprofloxacin Injection, the most frequently reported events, possibly, probably drug-related were: rash (1.8%), diarrhea (1.0%), and injection site pain (1.0%).

Local i.v. site reactions have been reported. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent i.v. administration is not contraindicated unless the reactions recur or worsen.

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

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

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

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

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

Hypersensitivity: rash. The following have been reported rarely: allergic reaction, anaphylactic/anaphylactoid reactions including facial, vascular and laryngeal edema, drug fever, haemorrhagic bullae and small nodules (papules) with crust formation showing vascular involvement (vasculitis), hepatitis, interstitial nephritis, petechiae (punctuate skin hemorrhages), pruritus, serum sickness-like reaction, Stevens-Johnson syndrome. 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).

I.V. 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) 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 has been reported very rarely: myasthenia (exacerbation of symptoms of myasthenia 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 has 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, strider, voice alteration.

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

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

Urogenital System: albuminuria, hematuria. The following have been reported rarely: abnormal kidney function, acute kidney failure, dysuria, leukorrhea, interstitial nephritis, 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: Tongue discoloration, colitis, gastritis.

Hemic and Lymphatic: Coagulation disorder, thrombocythemia.

Skin: Fungal dermatitis, pustular rash, sweating.

Metabolic: Hypernatremia, healing abnormal.

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 postmarketing 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 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 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.

Ciprofloxacin Injection should be administered by i.v. infusion over a period of 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation.

Adults

The recommended adult dosages of Ciprofloxacin Injection are:

Table 1: Recommended Adult Dosages of Ciprofloxacin Injection

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Moderate/ Severe/ Complicated	200 mg to 400 mg	q12h	400 mg to 800 mg
Respiratory Tract	Moderate/ Severe	400 mg	q8h to q12h	800 mg to 1200 mg
Skin or Skin Structure Blood Bone	Moderate	400 mg	q12h	800 mg
Intra-abdominal	Complicated	400 mg	q12h	400 mg q12h only when used in combination with metronidazole 500 mg i.v. q6h*
Empiric Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin Sodium	400 mg 50 mg/kg	q8h q4h	1200 mg Not to exceed 24 g/day

*

(1) Clinical success was demonstrated with a limited number of patients switched to oral therapy: (Ciprofloxacin Hydrochloride Tablets 500 mg p.o. q12h plus metronidazole 500 mg p.o. q6h) during day 3, 4 or 5 of therapy when able to take oral medication and having shown an initial clinical response to the intravenous therapy.

(2) See Metronidazole Product Monograph for Prescribing Information including cautionary statements.

(3) For information on ciprofloxacin plus metronidazole combination therapy, see **ACTION AND CLINICAL PHARMACOLOGY, HUMAN PHARMACOLOGY,** and **ADVERSE REACTIONS** sections of the Ciprofloxacin Injection Product Monograph.

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.

Sequential IV/PO Therapy

In patients receiving intravenous ciprofloxacin, oral ciprofloxacin may be considered when clinically indicated at the discretion of the physician. Clinical studies evaluating the use of sequential i.v./p.o. therapy in septicemia, however, have not been completed.

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/1.73 m^2	Maximum Daily Dose	Serum Creatinine Concentration mg/100 mL
	IV	
31 – 60	800 mg	1.4 – 1.9
≤ 30	400 mg	≥ 2.0

Maximum daily dose should not be exceeded when either creatinine clearance or serum creatinine are in the ranges stated above.

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

Females: 0.85 x the above value

Impaired Hepatic Function

No dosage adjustment is required.

Pediatric Use

The safety and efficacy of Ciprofloxacin Injection in individuals less than 18 years of age have not been established. Ciprofloxacin Injection should not be used in pediatric patients and adolescents. (See **WARNINGS**.)

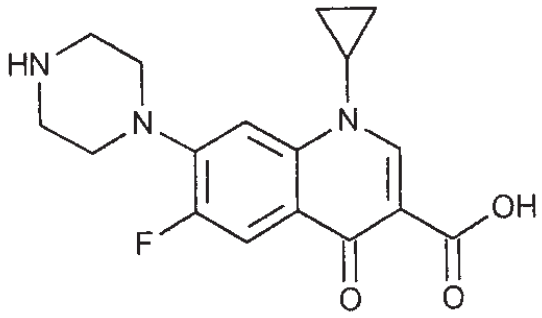
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Ciprofloxacin

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

Structural Formula:



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

Molecular Weight: 331.4

Description: Ciprofloxacin is a pale yellow to white crystalline powder which is soluble in dilute (0.1 N) hydrochloric acid and is practically insoluble in water and ethanol. Decomposition occurs between 261 – 265°C. pH of ciprofloxacin is 7.6 at 0.1 g/L water at 20°C. It has a pK_{a1} of 6.5 and pK_{a2} of 8.9 determined using a 3 x 10^{-4} M solution at 25°C. The lactate salt (for injection only) is formed *in situ* by the addition of lactic acid during the manufacturing process.

COMPOSITION

Injection

Ciprofloxacin	10 mg/mL
Lactic Acid (20%)	3.8 mg/mL
1 N Hydrochloric Acid	pH to 3.3 – 3.9
Water for Injection USP	q.s. to final volume

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature 15 – 30°C (56 – 86°F). Protect from light and freezing.

Single dose vial, discard unused portion.

PARENTERAL PRODUCTS

Intermittent Intravenous Infusion

Ciprofloxacin Injection should be administered only by intravenous infusion over a period of 60 minutes. The drug should not be given by rapid injection. Slow infusion of a dilute solution into a large vein will minimize patient discomfort and reduce the risk of venous irritation.

If Ciprofloxacin Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug. Ciprofloxacin Injection in the 10 mg/mL vials should be diluted to 1.0 – 2.0 mg/mL with the following recommended intravenous solutions, in PVC bag.

Recommended Intravenous Solutions for Dilution of Vials

0.9% Sodium Chloride Injection, USP

5% Dextrose Injection, USP

Ciprofloxacin Injection when diluted with the recommended intravenous solutions should be used within 24 hours at room temperature or 72 hours when refrigerated. Since ciprofloxacin is slightly light sensitive, the solutions should be protected from light during storage.

Table 3: Dilution Table for Vials

Vial Size	Vial Strength	Volume of Diluent To Be Used Per Vial	Approximate Concentration of Diluted Products
20 mL	200 mg, 1%	80 – 180 mL	1.0 mg/mL – 2.0 mg/mL
40 mL	400 mg, 1%	160 – 260 mL	1.3 mg/mL – 2.0 mg/mL

The intravenous dose should be prepared by aseptically withdrawing the appropriate volume of concentrate from the vials of Ciprofloxacin Injection. This should be diluted with the desired volume (80 – 260 mL) of a suitable intravenous solution (see **Recommended Intravenous Solutions**). The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. If this method or the "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Ciprofloxacin Injection.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

Ciprofloxacin Injection is available as 10 mg/mL ciprofloxacin (as ciprofloxacin lactate in Water for Injection) in single use vials as follows:

C309420 20 mL in a 20 mL vial packaged individually

C309440 40 mL in a 50 mL vial packaged individually

Vial stoppers do not contain natural rubber latex.

MICROBIOLOGY

The *in vitro* activity of ciprofloxacin against clinical isolates of gram-positive and gram-negative aerobic and anaerobic bacteria is shown in Table 4. 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 both 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 4: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin

		mg/L												
Genera or Species	**(Number of Strains)**	**0.02**	**0**	**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							
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								

Table 4: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin

		mg/L												
Genera or Species	**(Number of Strains)**	**0.02**	**0**	**0.06**	**0.122**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
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)	-(30)			13	50	93	100							
Pseudomonas aeruginosa (Bacteremic non-cystic strain)	-(30)		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								
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 5×10^3 to 5×10^6 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 5×10^3 to 5×10^6. *Streptococcus faecalis* showed a four-fold increase while the remainder showed only a two to three-fold increase (Table 5). 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 5). 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 5: 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**	**5×10^3**	**5×10^6**
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
Escherichia 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) 5×10^5 cfu/mL.

(b) No difference between the MICs 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 $< 1 \times 10^{-9}$ to 1×10^{-6}.

Susceptibility Testing

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (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 6: Daily Ranges for Ciprofloxacin for Quality Control Strains

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 (ATCC 49226)	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 i.v. ciprofloxacin.

Following a 60-minute intravenous infusion of 200 mg and 400 mg ciprofloxacin to 13 healthy male volunteers (18 – 40 years), the mean maximum serum concentrations achieved were 2.14 and 4.60 mg/L respectively; the concentrations at 12.0 hours were 0.11, 0.23 mg/L respectively (see Figure 1).

The pharmacokinetics of ciprofloxacin were linear over the dose range of 200 mg and 400 mg administered intravenously (see Table 7). At steady-state, the serum elimination half-life was approximately 5 – 6 hours and the total clearance around 35 L/hr was observed. Comparison of the pharmacokinetic parameters following the 1st and 5th i.v. doses on a 12-hour regimen indicated no evidence of drug accumulation.

An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours, for 6 doses, to 12 healthy male volunteers (18 – 40 years) has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by a 500 mg oral dose given every 12 hours. 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.

An infusion of 200 mg ciprofloxacin given every 12 hours produces an AUC equivalent to that produced by a 250 mg oral dose every 12 hours.

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

Table 7: 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
$t_{1/2}$ (hr)	4.19	4.87	5.34	3.4	3.5
AUC $_{0\rightarrow\infty}$ (mg·hr/L)	5.43	10.60	15.03	5.24	11.69
t_{max} (hr)	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.

Table 8: Mean Pharmacokinetic Parameters of Ciprofloxacin and Metronidazole at Steady-State in Healthy Volunteers

REGIMEN	AUC (mg·hr/L)	C_{max} (mg/L)	t_{max} (h)
(i) When administered alone			
Ciprofloxacin 500 mg p.o. q12h	13.7 (AUC $_{0\rightarrow12}$)	2.97	1.23
Ciprofloxacin 400 mg i.v. q12h	12.7 (AUC $_{0\rightarrow12}$)	4.56	1
(ii) When administered as ciprofloxacin 500 mg p.o. q12h in combination with metronidazole 500 mg p.o. q6h			
Ciprofloxacin	12.6 (AUC $_{0\rightarrow12}$)	2.73	1.3
Metronidazole	156.3 (AUC $_{0\rightarrow6}$)	31.3	1.71
(iii) When administered as ciprofloxacin 400 mg i.v. q12h in combination with metronidazole 500 mg i.v. q6h			
Ciprofloxacin	15.9 (AUC $_{0\rightarrow12}$)	5.21	1
Metronidazole	153.0 (AUC $_{0\rightarrow6}$)	33.6	1

Note: Following the repeated dosing of metronidazole 500 mg i.v. tid, the peak and minimum mean plasma metronidazole concentrations, at steady-state, were 26 µg/mL and 12 µg/mL respectively.

Figure 1: Mean Serum Ciprofloxacin Concentration (mg/L) vs. Time After a Single Intravenous Dose Administered Over 60 Minutes

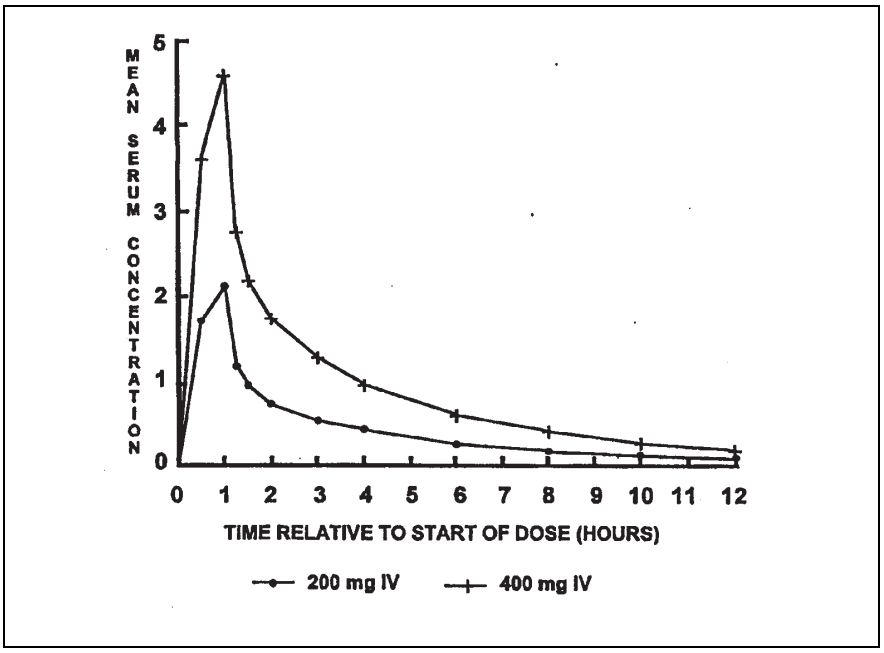


Table 9: Mean Urinary Excretion of Ciprofloxacin

	Hours After Administration of a Single Dose			
	0 – 2	**2 – 4**	**4 – 8**	**8 – 12**
Urine Concentration mg/L (± S.D.)				
250 mg p.o.	205 (± 89)	163 (± 145)	101 (± 65)	32 (± 28)
500 mg p.o.	255 (± 204)	358 (± 206)	117 (± 86)	26 (± 10)
750 mg p.o.	243 (± 143)	593 (± 526)	169 (± 131)	55 (± 36)
200 mg i.v.	335.2 (± 61.5)	99.9 (± 16.0)	71.7 (± 10.9)	31.24 (± 4.06)
400 mg i.v.	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)	8.9 (± 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 i.v.	58.8 (± 9.3)	13.6 (± 3.2)	14.1 (± 9.0)	7.5 (± 2.5)
400 mg i.v.	125.0 (± 7.2)	24.1 (± 4.7)	35.1 (± 12.7)	15.7 (± 3.9)

Note: IV dose administered over 30 minutes.

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 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 i.v. dose, urine concentrations of ciprofloxacin usually exceed 200 µg/mL during the first two hours after dosing, and are generally greater than 10 µg/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 i.v. 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.

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 10: 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
t_{max} (hr)	1.2 ± 0.3	1.2 ± 0.1
$t_{1/2}$ (hr)	3.7 ± 0.9	3.3 ± 0.6
Total AUC (mg·h/L)	7.25 ± 2.45	5.29 ± 1.21
% Dose Urinary Recovery after 24 hours	43	43

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. This

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

The pharmacokinetics of ciprofloxacin following multiple i.v. doses were compared in subjects with normal renal function and in subjects with various degrees of renal impairment (see Table 11, Groups 1 – 4). Patients with renal insufficiency had significantly increased concentrations of ciprofloxacin, Ml and M2 metabolites and decreased renal clearances.

Results of studies in patients on peritoneal dialysis and on hemodialysis show that very little ciprofloxacin is removed by dialysis.

An open-label crossover study was conducted in eight peritoneal dialysis patients. Patients received a single dose of i.v. ciprofloxacin on two separate occasions, once with frequent dialysis (fluid exchange done at 4, 8, 12, and 24 hours) and once with delayed dialysis (fluid exchange at 12 and 24 hours). Pharmacokinetic parameters for ciprofloxacin, Ml and M2 metabolites were not significantly different for frequent versus delayed dialysis, except that dialysate clearances for ciprofloxacin and M2 were higher when dialysis was done frequently. Group 5 in Table 11 shows the pharmacokinetic results for the frequent dialysis group.

In an open-label crossover study, seven hemodialysis patients received a single dose of i.v. ciprofloxacin on two separate occasions, once immediately after hemodialysis, and once two hours before hemodialysis. The results demonstrated that the pharmacokinetic parameters were not significantly different between the two treatments for ciprofloxacin, Ml and M2 metabolites. Group 6 in Table 11 shows the pharmacokinetic results for the group dosed two hours before hemodialysis.

Table 11: Mean Pharmacokinetic Parameters for Ciprofloxacin and Metabolites M1 and M2 Following IV Dosing in Healthy Volunteers, Patients with Renal Insufficiency, Peritoneal Dialysis Patients, and Hemodialysis Patients

Group	Creatinine Clearance mL/min/1.73m2	IV Ciprofloxacin Dose	Parameter								
			Ciprofloxacin			M1 (desethyleneciprofloxacin)			M2 (sulfociprofloxacin)		
			$AUC_{0\rightarrow\infty}$ (mg·hr/L)	Cl_r (L/hr)	$t_{1/2}$ (hr)	$AUC_{0\rightarrow\infty}$ (mg·hr/L)	Cl_r (L/hr)	$t_{1/2}$ (hr)	$AUC_{0\rightarrow\infty}$ (mg·hr/L)	Cl_r (L/hr)	$t_{1/2}$ (hr)
1	> 90	400 mg q8h x 11	10.2	20.3	4.59	0.19	19.9	5.04	0.98	19.5	2.33
2	61 – 90	400 mg q8h x 11	15.4	10.9	5.23	0.34	10.8	8.14	1.50	10.7	3.12
3	31 – 60	400 mg q12h x 8	21.5	6.91	5.72	0.57	7.1	9.10	4.21	6.52	5.25
4	≤ 30	300 mg q12h x 8	30.1	1.36	8.33	1.09	1.7	15.2	13.0	1.09	13.8
5	chronic renal failure patients on peritoneal dialysis	400 mg single dose	38.7	0.098	8.39	4.49	0.074	28.6	54.8	0.08	22.6
6	chronic renal failure patients on hemodialysis	400 mg single dose	38.4	0.11	11.4	2.05	0.087	11.6	29.9	0.073	13.1

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 Hydrochloride Tablets 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.

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.

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 hour. 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 third, slowly equilibrating tissue compartment with relatively slow intercompartmental clearance. This would contribute to the prolonged terminal half-life (4 to 5 h) of ciprofloxacin i.v. The results of this study were as follows:

Volume of distribution at steady-state (V_{ss}) was determined to be between 2.0 and 2.9 L/kg. Volumes in each compartment were determined to be as follows: central compartment 0.2 – 0.4L/kg , peripheral V_2 0.6 – 0.8 L/kg and peripheral V_3 1.2 – 1.6 L/kg.

Table 12 summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

Table 12: 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 p.o.	1.4 ± 0.36	2.3 ± 0.7	1 – 6
Bone	4	750 mg p.o.	1.4 ± 1.0	2.9 ± 2.2	2 – 4
Gynecological Tissue	18	500 mg p.o.	1.3 ± 0.66 to 1.6 ± 0.97	1.4 ± 0.87	2 – 4
Prostatic Tissue	1	500 mg p.o.	3.76	1.84	2.5
Muscle	4	250 mg p.o.	2.4 ± 1.0	2.9 ± 2.2	2 – 4
Nasal Secretions	20	500 mg p.o.	1.4 ± 0.81	1.8 ± 0.48	1 – 3
Bronchial Tissues	10	200 mg i.v.	3.94 ± 2.5	1.62 ± 0.7	0.97
Vagina	18	100 mg i.v.	1.13 ± 0.2	0.61 ± 0.12	0.5
Ovary	18	100 mg i.v.	1.00 ± 0.23	0.61 ± 0.12	0.5

TOXICOLOGY

Acute Toxicity

Table 13: Summary of Acute Toxicology in Animals

Species	Sex	Route of Administration	LD_{50}* mg/kg	95% confidence interval
Mouse	M	p.o.	5000	
Mouse	F	p.o.	Approx. 5000	
Mouse	M	i.v.	296.5	275 – 321
Mouse	F	i.v.	291.5	278 – 315
Rat	M	p.o.	5000	
Rat	F	p.o.	5000	
Rat	M	i.v.	147	130 – 164
Rat	F	i.v.	144	130 – 157
Rabbit	M	p.o.	Approx. 2500	
Rabbit	F	i.v.	Approx. 125	
Dog	M/F	p.o.	Not determinable, vomiting and regurgitating of the test substance	
Dog	M/F	i.v.	Approx. 250	

* Dosages in the toxicology section are expressed in terms of ciprofloxacin.

The dog regurgitated the substances to a large extent after high oral doses, so that neither symptoms of intoxication nor the LD_{50} could be determined.

The symptoms observed in the other species consisted of reduced orientation and motility, tonic-clonic convulsions, and gasping for breath at high doses. Cyanosis and narrowed palpebral fissures were observed in mice and rats treated with 5000 mg/kg orally.

Short-Term Toxicity

Groups of 10 male and 10 female Wistar rats each, strain Bor:WISW, were given ciprofloxacin hydrochloride in doses of 0, 5, 20, or 80 mg/kg/day intraperitoneally for 4 weeks. After administration of 80 mg/kg/day, evidence of mechanically caused nephropathy was found. This was associated with a slight effect on the kidney function (increased BUN.) Crystal-like precipitates were found in the distal tubules and were probably responsible for the mechanical tubule obstruction. The urine sediment was found also to contain crystals. On the basis of morphological criteria, the crystalline precipitates in the tubule lumens and those in the urine sediment were regarded as identical. They were probably caused by the low solubility of the ciprofloxacin at neutral pH values. Groups of 2 male and 2 female beagles each were given ciprofloxacin hydrochloride orally in doses of 0, 40, or 80 mg/kg/day for 4 weeks. Ciprofloxacin was administered orally, in gelatin capsules. Both doses produced swelling of the soft tissue in the region of the head, reddening, and pruritus after the very first dose. This oral intolerability improved substantially after the administration of ciprofloxacin in lacquered capsules. All the other investigations, haematological, clinical chemistry and urine analyses did not reveal any ciprofloxacin-related alterations. Pathological-anatomical and histopathological examinations likewise did not reveal any damage.

Groups of 2 male and 2 female Rhesus monkeys were given ciprofloxacin hydrochloride orally in doses of 0 or 15 mg/kg/day for 4 weeks. The appearance and behaviour of the animals, food and water intake, body weight developments, laboratory investigations, pathological-anatomical and histopathological examinations were all unaffected by treatment.

Long-Term Toxicity

In a study on SPF rats, strain Bor:WISW, groups of 20 male and 20 female animals each were given ciprofloxacin hydrochloride in oral doses of 0, 20, 100 or 500 mg/kg/day for 6 months. Five animals from each group were sacrificed after 3 months and 15 animals per sex and per group were dosed for 6 months. No evidence of damage caused by ciprofloxacin was observed on clinical evaluation, or on the basis of haematological and clinical chemistry tests and urine analyses. The pathological-anatomical and histopathological examination likewise gave no indications of damage related to the use of ciprofloxacin and, in particular, no kidney damage was present. However, the acicular crystals described in the short-term rat study were found in the urine sediment of some animals on 500 mg/kg/day.

REPRODUCTIVE TOXICITY

Fertility Studies

Ciprofloxacin hydrochloride was administered to rats, strain Bor:WISW, (24 males and 60 females per group) by a stomach tube, in doses of 0, 10, 30, or 100 mg/kg/day. Treatment was commenced in the males 10 weeks before mating and in the females 3 weeks before mating and was continued in the females up to the 7th day of gestation. Doses up to 100 mg/kg/day ciprofloxacin had no effects on fertility; the intrauterine and postnatal development of the young and the fertility of the Fl generation were likewise unimpaired by ciprofloxacin.

Embryotoxicity Studies

(a) Mouse

In a study on mice, strain BOC:NMRI, (25 per group), ciprofloxacin hydrochloride was given orally by stomach tube, in doses of 0, 10, 30 or 100 mg/kg/day from the 6th to the 15th day of gestation. Caesarean sections were performed on the 18th day of gestation. None of the doses tested caused either embryotoxic or teratogenic effects. The postnatal development of the offspring of all groups was also unaffected.

(b) Rats

In a study on rats, strain Bor:WISW, (15 per group) oral doses of 0 or 100 mg/kg/day were administered from the 6th to the 15th day of gestation. Rats were allowed to litter normally. The result of this study also indicated that the dose of 100 mg/kg/day had no embryotoxic or teratogenic effects. In a parenteral study on rats, strain BOC:WISW, (25 per group) ciprofloxacin hydrochloride at doses of 0, 3, 10, or 30 mg/kg/day was administered intravenously from day 6 to day 15 of gestation. Caesarean sections were performed on the 20th day of gestation. In addition, 2 groups of animals were given doses of 0 or 30 mg/kg/day for the same period but were allowed to litter normally and to rear their young for a period of 3 weeks. It was found that all the doses tested had neither embryotoxic nor teratogenic effects. No effects on the postnatal development of the reared young were observed.

(c) Rabbits

In a study on rabbits, strain CHBB:HM (12 per group) ciprofloxacin hydrochloride was given orally in doses of 0, 10, 30, or 100 mg/kg/day. For each dose, the animals were divided into 3 subgroups each treated for periods of 5 days: one subgroup from day 6 to day 10, one subgroup from day 10 to day 14, and one subgroup from day 14 to day 18 of gestation. Caesarean sections were performed on the 29th day of pregnancy. The dose of 100 mg/kg impaired digestion as evidenced by development of diarrhea, constipation and reduced food or water intake and as a result influenced body weight development of the dams. Increased rates of resorption, lower numbers of foetuses and lower foetal weights were observed and believed to be due to maternal toxicity. There was no evidence of embryotoxicity or teratogenicity.

In a parenteral study on rabbits, strain CHBB:HM, (12 per group) ciprofloxacin (lactate) at doses of 0, 2.5, 7, or 20 mg/kg/day was administered intravenously into an ear vein. Sequential treatment identical with that performed in the oral study was used. None of the doses tested caused maternal intolerance or any embryotoxic or teratogenic effects on the young.

Perinatal and Postnatal Studies

Pregnant SPF rats, strain Mura:WIST, (50 per group) were given ciprofloxacin hydrochloride orally in doses of 0, 10, 30, or 100 mg/kg/day. Treatment of the dams commenced on the 16th day of gestation. Caesarean sections were performed on 50% of the dams in each group on the 20th day of gestation. The remaining 50% of the dams in each group were allowed to litter naturally and to rear their young. Treatment was continued until the 21st day of lactation for this subgroup. None of the doses tested had any influence on the perinatal or postnatal development; no significant findings compared to the controls were found either in the caesarean section groups or in the groups in which the young were reared.

Female SPF rats, strain Bor:WIST, (50 per group) were given ciprofloxacin hydrochloride subcutaneously in doses of 0, 3, 10, or 30 mg/kg/day. Ciprofloxacin had no effect either on the late intrauterine development of the foetuses, the course of birth, postnatal development, or the fertility of the Fl generation. The histological examination of the joints of the young, performed at the end of the weaning period, did not reveal any damage to the articular cartilage.

MUTAGENICITY STUDIES

In vitro (see Table 14 for details)

The *Salmonella*/microsome test (the Ames test) was used to test for point-mutagenic effects. No mutagenicity could be attributed to ciprofloxacin using this standard test.

To investigate the potential effect on mammalian DNA, the unscheduled DNA synthesis (UDS) test on rat (F-344) hepatocytes, the mouse lymphoma test and hamster V79 (HGPRT locus) assay were used. The UDS test and the mouse lymphoma test were positive. The hamster V79 assay was negative.

In vivo (see Table 14 for details)

The micronucleus test was used for microsomal mutations in somatic tissue, and the dominant lethal test, for potential influence on damage-susceptible germ-cell stages. No mutagenicity could be attributed to ciprofloxacin using these two standard tests.

In vivo UDS test, in F-344 rat, gave no indication of DNA repair following a four-hour exposure to ciprofloxacin.

Table 14: Mutagenicity Studies Summary

***In vivo* Test**	**Strain**	**Positive Control and Dose**	**Ciprofloxacin Dose**	
Micronucleus Test	Bor:NMRI mice	Endoxan - 72.5 µg/kg once, oral	4,000 mg/kg ---------- 1,000 mg/kg 2,000 mg/kg 4,000 mg/kg	one, oral ---------- one, oral one, oral one, oral
Dominant Lethal Test	Bor:NMRI mice	Negative Control Only	4,000 mg/kg	one, oral
Rat Hepatocyte DNA Repair Test	F344 Male Fisher rat	2-acetylaminofluorene 10 mg/kg i.v.	30 mg/kg	one, i.v.
In vitro Test	**Positive Control and Concentration**		**Ciprofloxacin Concentration**	
Salmonella/Microsome Test (Ames)	Endoxan Trypaflavine 2-Aminoanthracene	145 µg/plate 50 µg/plate 3 µg/plate	0.016– 10.0 µg/plate	
Unscheduled DNA Synthesis Test (UDS)	2-Amino fluorene Fluorene	10^{-5} M 10^{-5} M	5 x 10^{-1} mg/mL to 1.25 x 10^{-2} mg/mL	
Mouse Lymphoma Test	Ethylmethane sulfonate Methylcholanthrene	0.3 – 0.4 µL/mL 2 – 4 µg/mL	10 – 500 µg/mL	
Hamster V79 HGPRT Assay	Ethylmethane sulfonate 9,10-Dimethy-1,2-benzenthracene	8 mM 15 µg/mL	70 – 700 µg/mL	

Joint and Oculotoxicity

Investigations with rats, strain Bor:WISW, weaned piglets German Landschwein breed, and purebred beagle dogs were carried out for possible arthropathogenic and oculotoxic potential.

Groups of 2 male and 2 female weaned piglets each were treated orally with ciprofloxacin hydrochloride for 16 successive days at doses of 0, 20, or 50 mg/kg/day. Autopsy was performed on the 17th day. An additional group received 50 mg/kg/day for 16 days and were kept for a 17-day treatment-free period before autopsy. Histopathological examinations did not show any alterations in the hip and knee joints.

Groups of 10 male and 10 female juvenile Wistar rats, strain Bor:WISW, aged between 4 and 5 weeks were given ciprofloxacin hydrochloride once a day by a stomach tube in doses of 0, 100, 250, or 500 mg/kg/day over a period of 10 days. In addition to the central question of joint tolerability, specific ophthalmoscopic and histopathological eye examinations were performed to assess the possibility of oculotoxicity. Ciprofloxacin induced marginal degenerative damage to the articular cartilage after the administration of the highest dose (500 mg/kg) and only in 1 of the 20 animals used. Doses up to 250 mg/kg/day were tolerated without any harmful effects. Ciprofloxacin caused no discernible ophthalmoscopic or histopathological damage to the eye.

In the dog study, groups of 2 male and 2 female beagles each, aged between 13 and 14 weeks were used. Ciprofloxacin hydrochloride was administered in gastric-juice-resistant gelatin capsules at doses of 0, 30, 70 or 100 mg/kg/day for 4 weeks. Histopathological examination revealed primary degenerative articular changes in the knee joint and hip joint cartilages at all doses tested. Severity of degenerative changes was dose-related with 100 mg/kg resulting in moderate primary degenerative articular cartilage changes in the knee-joint cartilage while 30 mg/kg resulted in slight focal degenerative change in the tibial knee-joint cartilage. No treatment-related ophthalmological changes were found.

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