PRODUCT MONOGRAPH

[Pr]CIPROFLOXACIN

(Ciprofloxacin Hydrochloride Tablets)

100, 250, 500 and 750 mg

Antibacterial Agent

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DATE OF PREPARATION:
May 22, 2012

Control No.: 155344

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

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

Distribution

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

Metabolism

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

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. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of ciprofloxacin following administration of a single (1 x 750 mg tablet) dose of Ciprofloxacin and Cipro® were measured and compared. The results are summarized as follows:

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Means (%)
	CIPROFLOXACIN	CIPRO®‡	
AUC_T (µg•hr/mL)	12.96 13.36 (26)	12.15 12.77 (31)	106.6
AUC_I (µg•hr/mL)	13.44 13.86 (26)	12.71 13.31 (30)	105.7
C_{max} (µg/mL)	2.67 2.75 (21)	2.52 2.68 (32)	106.2
T_{max}* (hr)	1.42 (0.60)	1.56 (0.50)	-
$t_{1/2}$* (hr)	5.40 (1.01)	5.87 (1.53)	-
* For the T_{max} and $t_{1/2}$ parameters, these are the arithmetic means (standard deviations). ‡ Cipro (Miles) from a Canadian pharmacy.			

INDICATIONS AND CLINICAL USES

CIPROFLOXACIN (ciprofloxacin hydrochloride) may be indicated for the treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

Respiratory Tract Infections

Acute exacerbation of chronic bronchitis caused by:

Haemophilus influenzae

Moraxella catarrhalis

Acute pneumonia caused by:

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Staphylococcus aureus

Acute sinusitis caused by:
Haemophilus influenzae
Moraxella catarrhalis

Due to the nature of the underlying conditions which usually predispose patients to pseudomonas infections of the respiratory tract, bacterial eradications may not be achieved in patients who display clinical improvement despite evidence of *in vitro* sensitivity. In patients requiring subsequent courses of therapy, CIPROFLOXACIN should be used alternately with other antipseudomonal agents. Some strains of *Pseudomonas aeruginosa* may develop resistance during treatment. Therefore, susceptibility testing should be performed periodically during therapy to detect the emergence of bacterial resistance.

Urinary Tract Infections

Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis, pyelonephritis, and pyelitis caused by:
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Morganella morganii
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus faecalis

Acute uncomplicated cystitis:

in females caused by *Escherichia 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

Staphylococcus aureus

Serratia marcescens

Infectious Diarrhea (when antibacterial therapy is indicated)

Caused by:

Campylobacter jejuni

Escherichia coli (enterotoxigenic strains)

Shigella dysenteriae
Shigella flexneri
Shigella sonnei

Meningococcal Carriers

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

Typhoid Fever (enteric fever)

Caused by:
Salmonella paratyphi
Salmonella typhi

Uncomplicated Gonorrhea

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

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

CONTRAINDICATIONS

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

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

WARNINGS

The safety of CIPROFLOXACIN (ciprofloxacin hydrochloride tablets) 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, 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.

Cardiac Disorders

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

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 thoughts or acts. In rare cases, depression or psychosis can progress to self-endangering behaviour. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. 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).

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 (eg, theophylline, methylxanthines, caffeine, duloxetine, clozapine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions).

Gastrointestinal

Clostridium difficile-associated disease

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

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

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

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 (eg, 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.

Interaction With Tests

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

Musculoskeletal

Rupture of the shoulder, hand and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including

ciprofloxacin. CIPROFLOXACIN should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPROFLOXACIN should be discontinued if the patient experiences pain, swelling, inflammation, or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

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

***Streptococcus pneumoniae* Infections**

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

PRECAUTIONS

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

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 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 CIPROFLOXACIN (ciprofloxacin hydrochloride) in pregnancy has not yet been established. CIPROFLOXACIN should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus (see WARNINGS). Ciprofloxacin has been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing Women

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

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 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

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

Drug Interactions

Caffeine and Other Xanthine Derivatives

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

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

Class IA or III Antiarrhythmics

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

Clozapine

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

Cyclosporine

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

Duloxetine

In clinical studies it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ferrous Sulfate

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

Food and Dairy Products

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

Glyburide

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

Histamine H2-receptor Antagonists

Histamine H2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Lidocaine

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

Methotrexate

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

Metoclopramide

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

Multivalent Cations

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-

containing products such as magnesium/aluminum antacids, polymeric phosphate binders such as sevelamer, lanthanum carbonate, sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, mineral supplements or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.

NSAID

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

Probenecid

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

Ropinirole

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

Sildenafil

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

Theophylline

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

Tizanidine

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

Vitamin K Antagonists

Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (eg, warfarin and acenocoumarol).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During worldwide clinical investigation (1991), 16,580 courses of ciprofloxacin treatment were evaluated for drug safety.

The incidence of adverse reactions was 8.0%. 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 treatment during clinical trials and subsequent post-marketing surveillance are as follows:

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

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

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

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

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

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

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

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, stridor, voice alteration.

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

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

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

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

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

The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide 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, peripheral neuropathy, phobia, pleural effusion, polyneuropathy, polyuria, postural hypotension, pulmonary embolism, purpura, QT prolongation, renal calculi, respiratory arrest, respiratory distress, restlessness, rhabdomyolysis, torsades de pointes, toxic psychosis, unresponsiveness, urethral bleeding, urination (frequent), ventricular ectopy, ventricular fibrillation, ventricular tachycardia, vesicles, visual acuity (decreased) and visual disturbances (flashing lights, change in colour perception, overbrightness of lights).

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.

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

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

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 (ciprofloxacin hydrochloride) may be taken before or after meals. Absorption is faster on an empty stomach.

Patients should be advised to drink fluids liberally and avoid taking dairy products or antacids containing magnesium or aluminum.

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

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

Adults

The recommended dosages of CIPROFLOXACIN are:

Table 1: Recommended Oral Dosages

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Mild/Moderate Severe/Complicated	250 mg 500 mg	q12h q12h	500 mg 1000 mg
Chronic Bacterial Prostatitis	Asymptomatic/Mild/ Moderate	500 mg	q 12h	1000 mg
Respiratory Tract Bone & Joint Skin & Soft Tissue	Mild/Moderate Severe*/Complicated	500 mg 750 mg	q12h q12h	1000 mg 1500 mg
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q12h	1000 mg
Urogenital and Extragenital Gonorrhea	Uncomplicated	500 mg	once	500 mg
Typhoid Fever	Mild/Moderate	500 mg	q12h	1000 mg
Neisseria meningitidis Nasopharyngeal Colonization	Carrier State	750 mg	once	750 mg
Acute Sinusitis	Moderate	500 mg	q12h	1000 mg

* e.g. hospital-acquired pneumonia, osteomyelitis

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

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

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

Hemodialysis

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

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

Creatinine Clearance mL/sec =

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

Females: 0.85 x the above value.

In traditional units mL/min =

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

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).

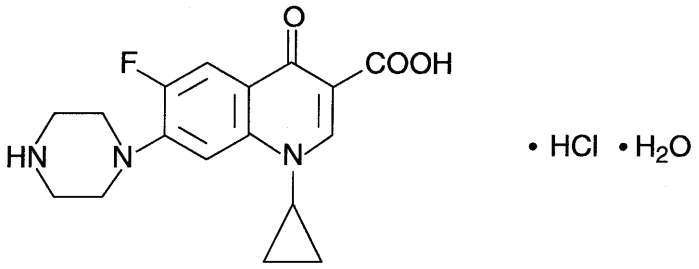
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper/Common Name: ciprofloxacin hydrochloride monohydrate

Chemical Name: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acidhydrochloride monohydrate.

Structural Formula:



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

Molecular Weight: 385.8

Description: Ciprofloxacin hydrochloride monohydrate 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. 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 3×10^{-4} M solution of 25˚C.

COMPOSITION

In addition to ciprofloxacin hydrochloride monohydrate, each tablet contains the non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature (15-30˚C).

AVAILABILITY OF DOSAGE FORMS

CIPROFLOXACIN 100 mg tablets: Each white, round, biconvex, film-coated tablet, engraved "APO" on one side and "100" on the other side contains ciprofloxacin hydrochloride monohydrate equivalent to 100 mg of ciprofloxacin. Available in bottles of 100.

CIPROFLOXACIN 250 mg tablets: Each white, round, biconvex, film-coated tablet, engraved "CIP" over "250" on one side and "APO" on the other side contains ciprofloxacin hydrochloride monohydrate equivalent to 250 mg of ciprofloxacin. Available in bottles of 100.

CIPROFLOXACIN 500 mg tablets: Each white, capsule-shaped, biconvex, film-coated tablet, engraved "APO-500" on one side and plain on the other contains ciprofloxacin hydrochloride monohydrate equivalent to 500 mg of ciprofloxacin. Available in bottles of 100 and 500.

CIPROFLOXACIN 750 mg tablets: Each white, capsule-shaped, biconvex film-coated tablet, engraved "APO-750" on one side and plain on the other contains ciprofloxacin hydrochloride monohydrate equivalent to 750 mg of ciprofloxacin. Available in bottles of 100.

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 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 3: CUMULATIVE PERCENT OF STRAINS INHIBITED AT THE INDICATED CONCENTRATIONS OF CIPROFLOXACIN (AS OF 1986)

		mg/L												
Genera or Species	**(Number of Strains)**	**0.015**	**0**	**0.1**	**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	55	75		95	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	50		75	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								
Propionibacterium spp.	42				2.4	28.6	88.1	92.9	100					

		mg/L												
Genera or Species	**(Number of Strains)**	**0.015**	**0**	**0.1**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
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								
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				2.4	28.6	88.1	92.9	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 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
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 x 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 $<1x10^{-9}$ to $1x10^{-6}$. 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 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		MIC (mg/L)
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 Strains

QC Strains	Disk Zone Diameter (mm)
S. aureus (ATCC 25923)	22 - 30
S. aureus (ATCC 29213)	-
E. coli (ATCC 25922)	30 - 40
P. aeruginosa (ATCC 27853)	25 - 33
N. gonorrhoeae (ATCC 49226)	48 - 58

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Effects on Histamine Release

Ciprofloxacin was administered intravenously to 9 anaesthetized dogs (initially with thiopental sodium at 25 mg/kg IV, followed by continuous infusion of a mixture of fentanyl 0.04 mg/kg/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 ($t_{1/2}$) were between 4 and 6 hours (See Table 6 and Figure 1).

Table 6: Pharmacokinetic Parameters Following a Single Oral Dose of Ciprofloxacin Tablets in Healthy Volunteers

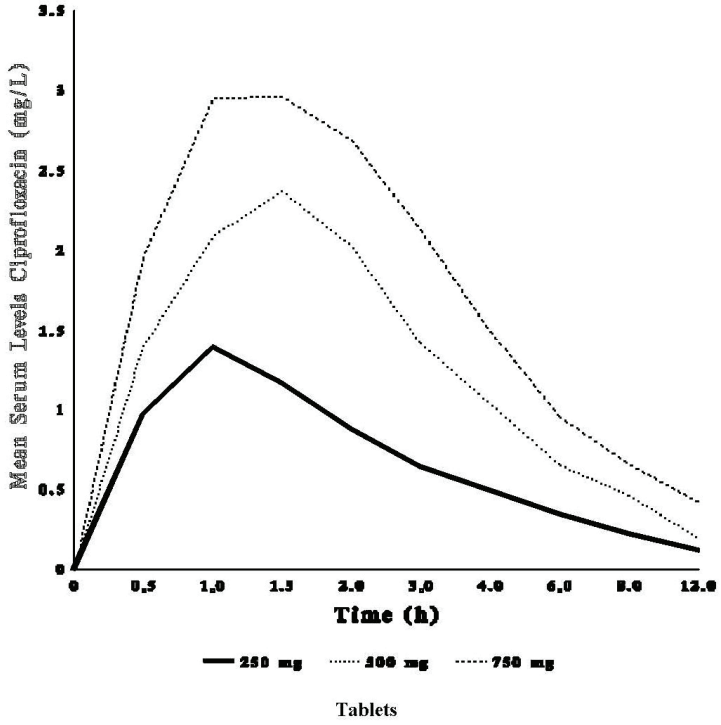
Dose	250 mg	500 mg	750 mg
C_{max} (mg/L)	1.42	2.60	3.41
$t_{½}$ (h)	4.19	4.87	5.34
$AUC_{0-\infty}$ (mg•h/L)	5.43	10.60	15.03
t_{max} (h)	1.11	1.11	1.56

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

Table 7: Mean Pharmacokinetic Parameters of Ciprofloxacin at Steady State in Healthy Volunteers

Regimen	$AUC_{0\text{-}12h}$ (mg•h/L)	C_{max} (mg/L)	t_{max} (h)
Ciprofloxacin 500 mg PO q12h	13.7	2.97	1.23

Figure 1: Mean Ciprofloxacin Serum Concentration After Single **Oral** Doses



A 500 mg oral dose, given as 10 mL of the 5% suspension (containing 250 mg ciprofloxacin/ 5 mL) is bioequivalent to the 500 mg tablet. A 10 mL volume of the 5% suspension (containing 250 mg ciprofloxacin/5 mL) is bioequivalent to a 5 mL volume of the 10% suspension (containing 500 mg ciprofloxacin/5 mL) (See Table 8).

Table 8: Summary Table of the Comparative Bioavailability Data Ciprofloxacin Oral Suspension vs Tablet, Geometric Mean and Arithmetic Mean (CV%)*, Single Doses in Healthy Volunteers

Parameter	500 mg Oral Suspension	500 mg Tablet	% Ratio of Geometric Means
$AUC_{0-\infty}$ (µg•h/mL)	11.81 12.19 (22.6)	12.04 12.28 (19.4)	0.98
AUC_I (µg•h/mL)	11.29 11.68 (23.1)	11.51 11.75 (19.9)	0.98
C_{max} (µg/mL)	2.18 2.23 (23.1)	2.36 2.39 (17.9)	0.92
t_{max} (h)*	1.62	1.22	-

* Arithmetic mean only

Metabolism and Excretion

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

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

Table 9 shows urinary recovery data from another trial where healthy subjects were administered a single dose of ciprofloxacin in tablet form (see Table 9).

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 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)

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.

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 Following Oral Administration of a Single 250 mg Tablet

Parameter	Elderly Volunteers (mean ± SD)	Younger Volunteers (mean ± SD)
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 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 11) were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment (see Group II, Table 11) and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis (see Group III, Table 11). 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 11).

TABLE 11 : Mean Pharmacokinetic Parameters for Ciprofloxacin Following a Single 250 mg Oral Dose in Healthy Volunteers and in Patients with Renal Insufficiency

Group	Creatinine Clearance ($mL/s/1.73m^2$) [$mL/min/1.73\ m^2$]	PARAMETER					
		C_{max} (mg/L)	t_{max} (h)	Half-life (h)	Total AUC (mg•h/L)	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 and Other Xanthine Derivatives

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

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

Class IA or III Antiarrhythmics

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

Multivalent Cations

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

Probenecid

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

Clozapine

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

Lidocaine

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

Ropinirole

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

Sildenafil

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

Vitamin K Antagonists

Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (eg, warfarin and acenocoumarol).

Serum Protein Binding

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

Tissue Concentrations

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

The distribution of ciprofloxacin was observed to be rapid in healthy volunteers receiving various single and multiple intravenous doses. Fitting the serum profile to a two-compartment model

provides a distribution phase with a half-life between 0.2 and 0.4 hours. The volume of distribution at steady state (Vd_{ss}) and Vd_{area} were between 1.7 and 2.7 L/kg respectfully. 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 (V2) with a high intercompartmental clearance rate, accounting for the rapid decline in ciprofloxacin concentrations in serum immediately following drug infusion; and a second, slowly equilibrating tissue compartment with relatively slow intercompartmental clearance. This would contribute to the prolonged terminal half-life (4 to 5 h) of ciprofloxacin IV.

The results of this study were as follows: volume of distribution at steady state (Vss) was determined to be between 2.0 and 2.9 L/kg. Volumes in each compartment were determined to be: central compartment 0.2 - 0.4, peripheral V2 0.6 - 0.8 and peripheral V3 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 Conc. (mg/kg or mg/L)	Mean Serum Conc (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
Gynaecological Tissue	18	500 mg PO	1.3 ± 0.66 to 1.6 ± 0.97	1.4 ± 0.87	2-4
Prostatic Tissue	1	500 mg PO	3.76	1.84	2.5
Muscle	4	250 mg PO	2.4 ± 1.0	2.9 ± 2.2	2-4
Nasal Secretions	20	500 mg PO	1.4 ± 0.81	1.8 ± 0.48	1-3
Bronchial Tissues	10	200 mg IV	3.94 ± 2.5	1.62±0.7	0.97
Vagina	18	100 mg IV	1.13±0.2	0.61±0.12	0.5
Ovary	18	100 mg IV	1.00±0.23	0.61±0.12	0.5

TOXICOLOGY

Acute Toxicity

Species	Mode of Administration	LD_{50} (mg/kg)
Mouse	PO	Approx. 5000
Rat	PO	Approx. 5000
Rabbit	PO	Approx. 2500
Mouse	IV	Approx. 290
Rat	IV	Approx. 145
Rabbit	IV	Approx. 125
Dog	IV	Approx. 250

Chronic Toxicity

Subacute Tolerability Studies Over 4 Weeks

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

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

Subchronic Tolerability Studies over 3 Months

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

Parenteral administration: Although the changes in the renal tubules observed in rats were in some cases very slight, they were present in every dose group. In monkeys they were found only in the

highest-dose group (18 mg/kg) and were associated with slightly reduced erythrocyte counts and hemoglobin values.

Chronic Tolerability Studies Over 6 Months

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

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

Carcinogenicity

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

Reproduction Toxicology

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

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

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

Mutagenicity

Eight in vitro mutagenicity tests have been conducted with ciprofloxacin. Test results are listed below:

Salmonella: Microsome Test (Negative)
E. coli: DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V79 Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae: Point Mutation Assay (Negative)
Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte Primary Culture DNA Repair Assay (LIDS) (Positive)

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

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

Special Tolerability Studies

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

Renal 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 does not immediately and automatically lead to kidney damage. In the animal studies, damage occured only after high doses, with correspondingly

high levels of crystalluria. For example, although they always caused crystalluria, even high doses were tolerated over 6 months without damage and without foreign-body reactions occurring in individual distal renal tubules.

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

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

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

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

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