

**PRODUCT MONOGRAPH**

**CIPRO<sup>®</sup>**

**(Ciprofloxacin Hydrochloride Tablets)**

**250 mg, 500 mg, 750 mg**

**U.S.P.**

**CIPRO<sup>®</sup> I.V.**

**(Ciprofloxacin Injection)**

**10 mg/mL in Water for Injection**

**Bayer Standard**

**CIPRO<sup>®</sup> I.V. MINIBAGS**

**(Ciprofloxacin Injection)**

**2 mg/mL in 5% Dextrose**

**Bayer Standard**

**CIPRO<sup>®</sup> ORAL SUSPENSION**

**(Ciprofloxacin Oral Suspension)**

**10g/100 mL**

**Bayer Standard**

**Antibacterial Agent**

**Bayer Inc.  
77 Belfield Road  
Toronto, Ontario  
M9W 1G6  
Canada**

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**[www.bayer.ca](http://www.bayer.ca)**

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

The pharmacokinetics of ciprofloxacin oral suspension 10% are virtually identical to those of tablets.

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 (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M 4, with the smallest quantity, is largely equivalent to norfloxacin in its antimicrobial activity.

### **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.

### **General**

Ciprofloxacin and metronidazole have been studied in combination and serum levels of ciprofloxacin are not significantly altered by metronidazole at the doses studied. Serum levels of metronidazole when administered orally at a dose of 500 mg q6h in combination with ciprofloxacin 500 mg PO q12h are:  $AUC_{0-6}$  156.3 mg.h/L,  $C_{max}$  31.3 mg/L and  $t_{max}$  1.71 hours. Serum levels of metronidazole when administered intravenously at a dose of 500 mg IV q6h in combination with ciprofloxacin 400 mg IV q12h are:  $AUC_{0-6}$  153.0 mg.h/L,  $C_{max}$  33.6 mg/L and  $t_{max}$  1.0 hours. (See **DOSAGE AND ADMINISTRATION** and **HUMAN PHARMACOLOGY**.)

Following infusion of 400 mg IV Ciprofloxacin every eight hours in combination with 50 mg/kg IV piperacillin sodium every 4 hours, mean serum ciprofloxacin concentrations were 3.02 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 IV 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

### A) Oral Administration

CIPRO<sup>®</sup> (ciprofloxacin hydrochloride tablets) and CIPRO<sup>®</sup> Oral Suspension (ciprofloxacin oral suspension) may be indicated for the treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

#### Respiratory Tract Infections

Acute exacerbation of chronic bronchitis caused by:

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Streptococcus pneumoniae*

Acute pneumonia caused by:

*Enterobacter cloacae*

*Escherichia coli*

*Haemophilus influenzae*

*Klebsiella pneumoniae*

*Proteus mirabilis*

*Pseudomonas aeruginosa*

*Staphylococcus aureus*

*Streptococcus pneumoniae*

Acute sinusitis caused by:

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Streptococcus pneumoniae*

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

*Serratia marcescens*

*Staphylococcus aureus*

**Infectious Diarrhea** (when antibacterial therapy is indicated)

Caused by:

*Campylobacter jejuni*

*Escherichia coli* (enterotoxigenic strains)

*Shigella dysenteriae*

*Shigella flexneri*

*Shigella sonnei*



**Meningococcal Carriers**

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

**Typhoid Fever** (enteric fever)

Caused by:

*Salmonella paratyphi*

*Salmonella typhi*

**Uncomplicated Gonorrhea**

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

**B) Intravenous Administration**

CIPRO® I.V. (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, CIPRO® 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 CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension 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**

CIPRO<sup>®</sup> (ciprofloxacin hydrochloride tablets), CIPRO<sup>®</sup> I.V. (ciprofloxacin injection) and CIPRO<sup>®</sup> Oral Suspension (ciprofloxacin oral suspension) are 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 CIPRO<sup>®</sup> (ciprofloxacin hydrochloride tablets), CIPRO<sup>®</sup> I.V. (ciprofloxacin injection) and CIPRO<sup>®</sup> Oral Suspension (ciprofloxacin oral suspension) in pediatric patients and adolescents (under the age of 18 years), pregnant women and nursing women has not yet**

**been established.** (See **PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Women.**) Damage to juvenile weight-bearing joints and lameness were observed both in rat and dog studies but not in weaned piglets. (See **TOXICOLOGY.**) Histopathological examination of the weight-bearing joints in immature dogs revealed permanent lesions of the cartilage.

### **CNS and Psychiatric Effects**

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and rarely, suicidal 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 (e.g., theophylline, methylxanthines, caffeine, duloxetine, clozapine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See **CONTRAINDICATIONS** and **PRECAUTIONS, Drug Interactions.**)

### **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.

## **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**.)

### **PRECAUTIONS**

**SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPRO® I.V. 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 (generally Achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids. At any sign of tendonitis (ie, painful swelling, inflammation), a physician should be consulted and the antibiotic treatment should be discontinued. Care should be taken to keep the affected extremity at rest and avoid any inappropriate exercise (as the risk for tendon rupture might increase otherwise). Ciprofloxacin should not be used in patients with a clear history of tendon disorders related to quinolone treatment because they may be at risk of developing tendon disorders again when re-exposed to a fluoroquinolone.

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 CIPRO<sup>®</sup> and CIPRO<sup>®</sup> I.V. 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 CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension in pregnancy have not yet been established. CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus. (See **WARNINGS**.) CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension have been shown to be non-embryotoxic and non-teratogenic in animal studies.

### **Nursing Women**

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from women taking ciprofloxacin, a decision should be made to discontinue nursing or to discontinue the administration of CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension, 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, CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension should be used with caution and at a reduced dosage in patients with impaired renal function. (See [DOSAGE AND ADMINISTRATION, HUMAN PHARMACOLOGY](#).)

### **Hepatic Impairment**

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

### **Ability to Drive and Operate Machinery**

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

**Sucrose load for oral suspension formulation**

As the oral suspension contains sucrose, it is unsuitable for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency. (See [PHARMACEUTICAL INFORMATION](#).)

**Dextrose load for intravenous solution formulation**

Ciprofloxacin infusion solution (bags) contain glucose. This should be taken into account in patients with diabetes mellitus. Glucose content is 5 g for the 100 mL bag and 10 g for the 200 mL bag. (See [PHARMACEUTICAL INFORMATION](#)).

**Drug Interactions****Caffeine**

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

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

**Ferrous Sulfate**

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

**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 H<sub>2</sub>-receptor Antagonists**

Histamine H<sub>2</sub>-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, sucralfate, Videx<sup>®</sup> (didanosine) chewable/buffered tablets or pediatric powder, mineral supplements or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.

**NSAID**

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

**Probenecid**

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

**Ropinirole**

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

**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 (see **ADVERSE REACTIONS**). If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage

adjustments made as appropriate.

### **Tizanidine**

In a clinical study in healthy subjects there was an increase in tizanidine serum concentrations (C<sub>max</sub> 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.**)

### **Warfarin**

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.

## **ADVERSE REACTIONS**

CIPRO<sup>®</sup> (ciprofloxacin hydrochloride tablets), CIPRO<sup>®</sup> I.V. (ciprofloxacin injection) and CIPRO<sup>®</sup> Oral Suspension (ciprofloxacin oral suspension) are generally well tolerated. During worldwide clinical investigation, 16,580 courses of ciprofloxacin treatment were evaluated for drug safety.

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

In orally treated patients enrolled in clinical trials, the most frequently reported events, possibly, probably drug-related were: nausea (1.3%), and diarrhea (1.0%).

In patients treated with CIPRO<sup>®</sup> I.V. 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 ciprofloxacin oral and i.v. 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  $\geq 0.01\%$   $< 0.1\%$ ): 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).

**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 have been reported very rarely: myasthenia (exacerbation of symptoms of myasthenia gravis).

There have been 54 reports of arthropathies with CIPRO<sup>®</sup>. 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 CIPRO<sup>®</sup>. In these instances, CIPRO<sup>®</sup> 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.

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

**Cardiovascular:** peripheral edema

**Digestive:** colitis, gastritis, tongue discoloration

**Hemic and Lymphatic:** coagulation disorder, thrombocythemia

**Skin:** fungal dermatitis, pustular rash, sweating

**Metabolic:** healing abnormal, hypernatremia

**Nervous:** dementia

**Urinary:** kidney tumour necrosis, urinary incontinence.

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

### **SYMPTOMS AND TREATMENT OF OVERDOSE**

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

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

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.

#### **Oral Administration**

CIPRO<sup>®</sup> (ciprofloxacin hydrochloride tablets) or CIPRO<sup>®</sup> Oral Suspension (ciprofloxacin oral suspension)<sup>A</sup> 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<sup>®</sup> (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 oral CIPRO<sup>®</sup> are:

**Table 1: Recommended Dosages for Oral CIPRO<sup>®</sup>**

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

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

<sup>A</sup> One teaspoon (5 mL) of 10% oral ciprofloxacin suspension = 500 mg of ciprofloxacin  
See Instructions below for USE/HANDLING

**Table 2: Use/Handling of Ciprofloxacin Suspension**

Dosage	Volume (mL) of 10 % Oral Suspension
250 mg	2.5 mL
500 mg	5 mL
750 mg	7.5 mL

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.

### **Instructions to the Pharmacist for Use/Handling of CIPRO<sup>®</sup> Oral Suspension:**

#### **Preparation of the suspension:**

1. The small bottle contains the ciprofloxacin microcapsules; the large bottle contains the diluent.
2. Open both bottles. Child-proof cap: Press down according to the instructions on the cap while turning to the left.
3. Pour the microcapsules completely into the large bottle of diluent. **Do not add water to the suspension.**
4. Close the large bottle completely according to the instructions on the cap and shake vigorously for about 15 seconds. The suspension is ready for use.

### **Instructions to the Patient for Taking CIPRO<sup>®</sup> Oral Suspension**

#### **Shake vigorously each time before use for approximately 15 seconds.**

Swallow the prescribed amount of suspension. Do not chew the microcapsules. Reclose the bottle completely after use according to instruction on the cap. The suspension is stable for 14 days when stored in a refrigerator or at room temperature (5-25°C). Store in an upright position. After treatment has been completed, any remaining suspension should not be reused.

### **Intravenous Administration**

Ciprofloxacin 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 CIPRO<sup>®</sup> I.V. (ciprofloxacin injection) are:

**Table 3: Recommended Adult Dosages of CIPRO<sup>®</sup> I.V. (Ciprofloxacin Injection)**

<b>Location of Infection</b>	<b>Type/Severity</b>	<b>Unit Dose</b>	<b>Frequency</b>	<b>Daily Dose</b>
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 IV q6h*
Empiric Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin Sodium	400 mg	q8h	1200 mg
		50 mg/kg	q4h	Not to exceed 24 g/day

\*1) Clinical success was demonstrated with a limited number of patients switched to oral therapy: (CIPRO<sup>®</sup> 500 mg PO q12h plus metronidazole 500 mg PO 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 CIPRO<sup>®</sup> plus metronidazole combination therapy, see **Action and Clinical Pharmacology**, **Human Pharmacology**, and **Adverse Reaction** sections of the Ciprofloxacin 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 I.V./P.O. 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 4: Maximum Daily Dose with Stated Creatinine Clearance or Serum Creatinine**

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

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

### ***Hemodialysis***

Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis. For hemodialysis patients, please follow dosing recommendations as described in **Table 4**. 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:  $\frac{\text{Weight (kg)} \times (140 - \text{age})}{49 \times \text{serum creatinine } (\mu\text{mol/L})}$

Females: 0.85 x the above value

In traditional units mL/min =

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

Females: 0.85 x the above value

### **Impaired Hepatic Function**

No dosage adjustment is required.

### **Pediatric Use**

The safety and efficacy of CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension in individuals less than 18 years of age has not been established. CIPRO<sup>®</sup>, CIPRO<sup>®</sup> I.V. and CIPRO<sup>®</sup> Oral Suspension should not be used in pediatric patients and adolescents. (See **WARNINGS**.)



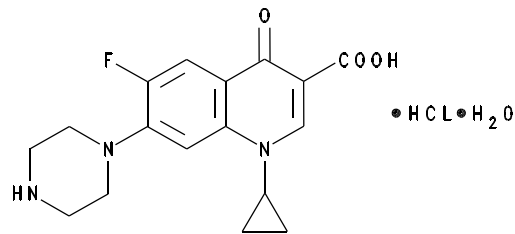
**PHARMACEUTICAL INFORMATION**

**DRUG SUBSTANCE**

**Proper Name:** Ciprofloxacin hydrochloride

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

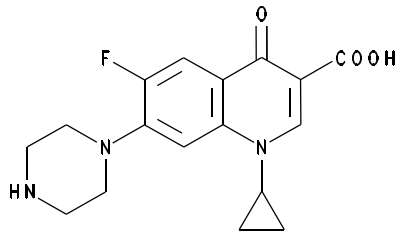
**Structural Formula:**



**Molecular Formula:** C<sub>17</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>3</sub> HCl H<sub>2</sub>O

**Molecular Weight:** 385.8

**Description:** Ciprofloxacin hydrochloride is a pale yellow crystalline powder. It is soluble in water. Its solubility in aqueous buffer of pH 7.4 at 21°C is 0.19 g/L, while the solubility is considerably higher at slightly acidic or slightly alkaline pH. At 140°C water of crystallization is lost. At 307°C decomposition takes place. The pH of ciprofloxacin hydrochloride is between 3 and 4.5 in a solution (1 in 40). The pK<sub>a1</sub> is 6.5 and pK<sub>a2</sub> is 8.9 determined using a 3 x 10<sup>-4</sup> M solution of 25°C.

**DRUG SUBSTANCE****Proper Name:** Ciprofloxacin**Chemical Name:** 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(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°C - 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  $3 \times 10^{-4}M$  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****Tablets**

Ciprofloxacin Hydrochloride

Microcrystalline Cellulose

Maize Starch

Colloidal Silicon Dioxide  
 Purified Water  
 Crospovidone  
 Magnesium Stearate  
 Titanium Dioxide  
 Methyl-hydroxypropylcellulose 2910-15  
 Polyethylene Glycol

**Injection**

Ciprofloxacin	10 mg/mL
Lactic Acid (20%)	3.72 mg/mL
1 N Hydrochloric Acid	pH to 3.3 - 3.9
Water for Injection USP	qs to final volume

**Minibags**

Ciprofloxacin	200 mg	400 mg
Dextrose (hydrous)	5.0 g	10.0 g
Lactic Acid (20%)	0.322 g	0.644 g
1 N Hydrochloric Acid	pH to 3.5-4.6	pH to 3.5-4.6
Water for Injection USP	qs to 100 mL	qs to 200 mL

**Oral Suspension**

A. Microcapsules

Ciprofloxacin “oral, new” micronized  
 Poly (ethyl acrylate methyl methacrylate) - dispersion 30%  
 Magnesium Stearate  
 Methyl-hydroxypropylcellulose  
 Polysorbate 20  
 Polyvidone 25

**B. Diluent**

Strawberry flavour 52312

Strawberry flavour 54267

Lecithin NF/Medium chain triglycerides

Medium chain triglycerides

Sucrose micronized

Water, purified

**STABILITY AND STORAGE RECOMMENDATIONS****Tablets:** Store below 30°C (86°F)**Vial:** Protect from light  
Store at controlled room temperature  
15-30°C (56-86°F)**Minibags:** Protect from light, excessive heat and freezing  
Store at controlled room temperature 15-25°C (56-77°F)  
Use promptly when pouch is opened**Oral Suspension:** The trade pack supplied to the Pharmacist (microcapsules and diluent in separate bottles) is to be stored at room temperature (15-25°C) and protected from freezing. Store in an upright position.

The freshly reconstituted suspension is stable for 14 days when stored in the refrigerator or at room temperature (5-25°C). Store in an upright position.

**Shake vigorously for 15 seconds each time before use.**

## **PARENTERAL PRODUCTS**

### **Intermittent Intravenous Infusion**

CIPRO® I.V. (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.<sup>34</sup>

If CIPRO® I.V. 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. Only CIPRO® I.V. (ciprofloxacin injection) in the 10 mg/mL vials should be diluted to 1.0 - 2.0 mg/mL with the following recommended intravenous solutions. CIPRO® I.V. MINIBAGS (ciprofloxacin injection) contain ciprofloxacin at 2.0 mg/mL and should be administered “as is”.

### **Recommended Intravenous Solutions for Dilution of Vials:**

Sterile Water for Injection, USP

0.9% Sodium Chloride Injection, USP

5% Dextrose Injection, USP

5% Dextrose in 0.225% Sodium Chloride Injection, USP

5% Dextrose in 0.45% Sodium Chloride Injection, USP

5% Dextrose in Electrolyte #75 Injection

10% Dextrose Injection

10% Fructose Injection

Ringer's Injection

Lactated Ringer's 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 5: 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

**Vials**

The intravenous dose should be prepared by aseptically withdrawing the appropriate volume of concentrate from the vials of CIPRO<sup>®</sup> I.V. This should be diluted with the desired volume (80-260 mL) of a suitable intravenous solution. (See **RECOMMENDED INTRAVENOUS SOLUTION.**) 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 CIPRO<sup>®</sup> I.V.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit.

**AVAILABILITY OF DOSAGE FORMS****Coated Tablets**

CIPRO<sup>®</sup> 250 - each round tablet is white to slightly yellowish. One side of the tablet is engraved with "CIP score 250" and the Bayer Cross on the other and contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin. Bottles of 100.

CIPRO<sup>®</sup> 500 - each oblong tablet is white to slightly yellowish. One side of the tablet is engraved with "CIP score 500" and Bayer on the other and contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin. Bottles of 100 and unit dose packages of 100.

CIPRO<sup>®</sup> 750 - each oblong tablet is white to slightly yellowish. One side of the tablet is engraved with "CIP score 750" and Bayer on the other and contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin. Bottles of 50 and unit dose packages of 100.

**CIPRO<sup>®</sup> I.V.**

Minibags - each mL contains 2 mg of ciprofloxacin in ready-to-use minibags of 100 mL and 200 mL.

**CIPRO<sup>®</sup> Oral Suspension**

Ciprofloxacin Oral Suspension is supplied as a 10% (10 g ciprofloxacin in 100 mL) strength. The drug product is composed of two components (microcapsules and diluent) which are mixed prior to dispensing. (See Instruction To The Pharmacist for Use/Handling).

**Table 6: CIPRO<sup>®</sup> Oral Suspension**

<b>Total Volume after Reconstitution</b>	<b>Ciprofloxacin Contents after Reconstitution</b>	<b>Ciprofloxacin Contents per Bottle</b>
100 mL	500 mg/5 mL	10,000 mg

**Store at room temperature (15-25°C) in an upright position.** Protect from freezing.

**Reconstituted product may be stored in a refrigerator or at room temperature (5-25°C) for 14 days.** Store in an upright position. A teaspoon is provided for the patient.

## MICROBIOLOGY

The *in vitro* activity of ciprofloxacin against clinical isolates of gram-positive and gram-negative aerobic and anaerobic bacteria is shown in [Table 7](#). 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 7: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin**

Genera or Species	(Number of Strains)	mg/L												
		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 cloacae	-49	61	86	96	100									
Escherichia coli	-203	84	92	93	96	98	99	100						
Flavobacterium breve	-3						66	100						
Fusobacterium spp.	-8					25	50		75	87.5	100			
Haemophilus ducreyi	-72	100												
Haemophilus influenzae	-50		90	100										
beta-lactamase positive														
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						



**Table 7: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin**

Genera or Species	(Number of Strains)	mg/L												
		0.015	0	0.1	0.12	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)			3	20	43	63	80	100						
Pseudomonas aeruginosa (Fibrocystic non-mucoid strain)	-(30)			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						31	87	100					
Streptococcus pneumoniae	-51					9	27	100						

**Table 7: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin**

		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
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  $5 \times 10^3$  to  $5 \times 10^6$  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  $5 \times 10^3$  to  $5 \times 10^6$ . *Streptococcus faecalis* showed a four-fold increase while the remainder showed only a two to three-fold increase (Table 8). 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 8). 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 8: Effect of Culture Medium Composition, pH and Inoculum Size On Antibacterial Activity of Ciprofloxacin**

Organism/Strain	MIC (mg/L)				
	pH <sup>a</sup>			Inoculum Size (cfu) <sup>b</sup>	
	4.8	7.3	8.8	$5 \times 10^3$	$5 \times 10^6$
<i>Staphylococcus aureus</i> K 734	4.0	0.5	0.5	0.25	0.5
<i>Staphylococcus epidermidis</i> H 846	2.0	0.25	0.25	0.125	0.25
<i>Streptococcus faecalis</i> 7149	8.0	1.0	1.0	0.5	2.0
<i>Escherichia coli</i> 2345	0.5	0.016	0.016	0.008	0.016
<i>Proteus mirabilis</i> 2349	1.0	0.03	0.016	0.008	0.03

<sup>a</sup> Mueller Hinton broth (BBL)  $5 \times 10^5$  cfu/mL.

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

### **Development of Resistance**

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

### **Susceptibility Testing**

**Dilution Techniques:** Quantitative methods are used to determine antimicrobial 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:

<b><u>MIC (µg/mL)</u></b>	<b><u>Interpretation</u></b>	
≤ 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:

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Enterococcus faecalis</i>	ATCC 29212	0.25 - 2.0
<i>Escherichia coli</i>	ATCC 25922	0.004 – 0.015
<i>Staphylococcus aureus</i>	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- $\mu$ g 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  $\mu$ g ciprofloxacin disk should be interpreted according to the following criteria:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\geq 21$	(S) Susceptible
16 - 20	(I) Intermediate
$\leq 15$	(R) Resistant

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- $\mu$ g ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

**Table 9: Daily Ranges for Ciprofloxacin for Quality Control Strains**

QC Strains	Disk Zone Diameter (mm)	MIC (mg/L)
<i>S. aureus</i> (ATCC 25923)	22 - 30	-
<i>S. aureus</i> (ATCC 29213)	-	0.25 - 1.0
<i>E. coli</i> (ATCC 25922)	30 - 40	0.008 - 0.03
<i>P. aeruginosa</i> (ATCC 27853)	25 - 33	0.25 - 1.0
<i>N. gonorrhoeae</i> (ATCC 49226)	48 - 58	$\leq$ 0.008

## PHARMACOLOGY

### ANIMAL PHARMACOLOGY

#### Effects on Histamine Release

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

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



### **Bronchodilatory Effects**

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

### **CNS Effects**

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

### **Gastrointestinal Effects**

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

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

### **Effect on Blood Glucose and Serum Triglycerides**

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

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

## HUMAN PHARMACOLOGY

### Pharmacokinetics

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

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of CIPRO<sup>®</sup> respectively to groups of 3 healthy male volunteers (age:  $22.8 \pm 3.5$  years, weight:  $68.5 \pm 9.4$  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 11.](#))

With oral administration, a 500 mg 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 10.](#))

**Table 10: 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 <sub>0-∞</sub> (µg•h/mL)	11.81	12.04	0.98
	12.19 (22.6)	12.28 (19.4)	
AUC <sub>t</sub> (µg•h/mL)	11.29	11.51	0.98
	11.68 (23.1)	11.75 (19.9)	
C <sub>max</sub> (µg/mL)	2.18	2.36	0.92
	2.23 (23.1)	2.39 (17.9)	
t <sub>max</sub> (hr)*	1.62	1.22	-

\* arithmetic mean only

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 2).

The pharmacokinetics of ciprofloxacin were linear over the dose range of 200 mg and 400 mg administered intravenously (see Table 11). 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 iv dose on a 12h 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 iv 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 11: 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 <sub>0-∞</sub> (mg•h/L)	5.43	10.60	15.03	5.24	11.69
$t_{max}$ (hr)	1.11	1.11	1.56	0.95	1.00

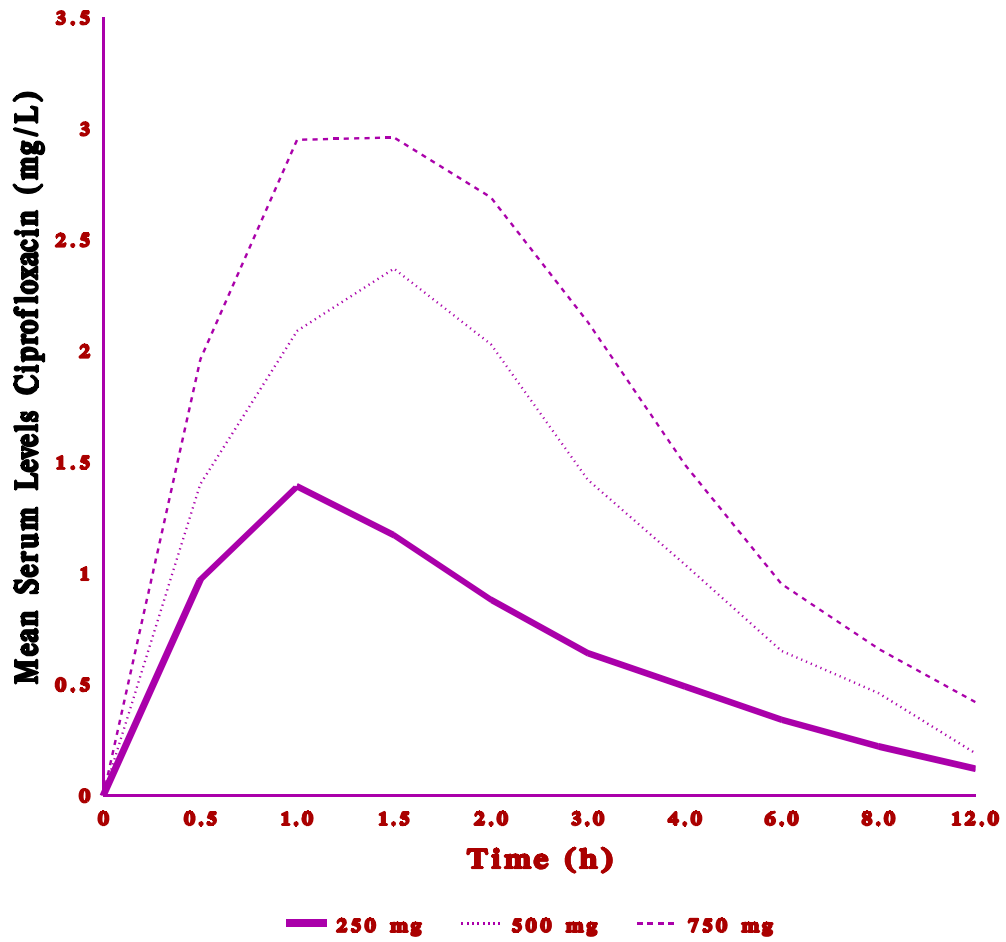
\* IV parameters following a 60-minute infusion period

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

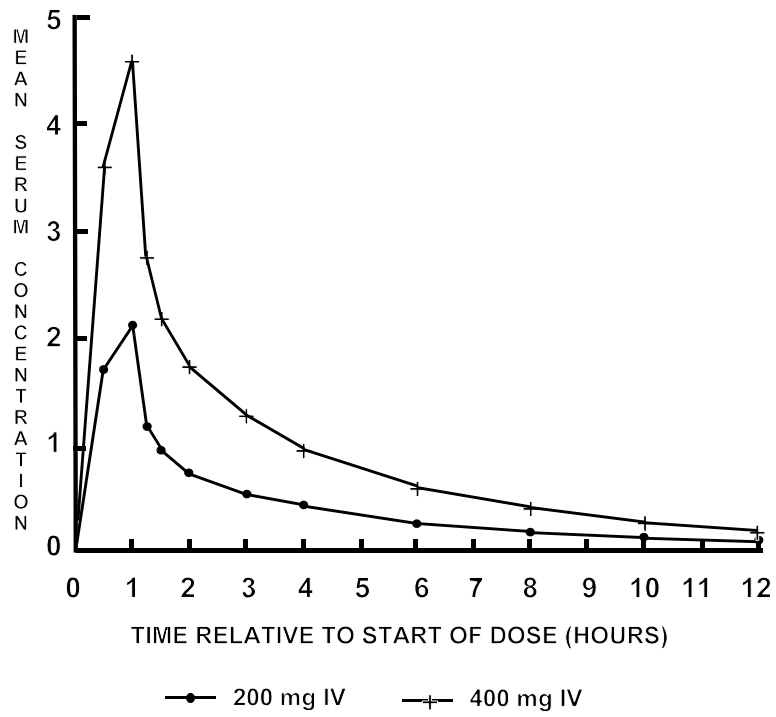
**Table 12: Mean Pharmacokinetic Parameters of Ciprofloxacin and Metronidazole at Steady State in Healthy Volunteers**

Regimen	AUC (mg•h/L)	C <sub>max</sub> (mg/L)	t <sub>max</sub> (h)
<b>(i) When administered alone</b>			
Ciprofloxacin 500 mg PO q12h	13.7 (AUC <sub>0-12</sub> )	2.97	1.23
Ciprofloxacin 400 mg IV q12h	12.7 (AUC <sub>0-12</sub> )	4.56	1.0
<b>(ii) When administered as Ciprofloxacin 500 mg PO q12h in combination with Metronidazole 500 mg PO q6h</b>			
Ciprofloxacin	12.6 (AUC <sub>0-12</sub> )	2.73	1.3
Metronidazole	156.3 (AUC <sub>0-6</sub> )	31.3	1.71
<b>(iii) When administered as Ciprofloxacin 400 mg IV q12h in combination with Metronidazole 500 mg IV q6h</b>			
Ciprofloxacin	15.9 (AUC <sub>0-12</sub> )	5.21	1.0
Metronidazole	153.0 (AUC <sub>0-6</sub> )	33.6	1.0

Note: Following the repeated dosing of metronidazole 500 mg IV tid, the peak and minimum mean plasma metronidazole concentrations, at steady-state, were 26 µg/mL and 12 µg/mL respectively.<sup>36</sup>

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

**Figure 2**  
**Mean Serum Ciprofloxacin Serum Concentration (mg/L) vs Time**  
**after A Single Intravenous Dose Administered over 60 Minutes**



**Table 13: Mean Urinary Excretion of Ciprofloxacin**

<b>Hours After Administration of a Single Dose</b>				
	<b>0 - 2</b>	<b>2 - 4</b>	<b>4 - 8</b>	<b>8 - 12</b>
<b>Urine Concentration mg/L (± S.D.)</b>				
250 mg po	205 (±89)	163 (±145)	101 (±65)	32 (±28)
500 mg po	255 (±204)	358 (±206)	117 (±86)	26 (±10)
750 mg po	243 (±143)	593 (±526)	169 (±131)	55 (±36)
200 mg iv	335.2 (±61.5)	99.9 (±16.0)	71.7 (±10.9)	31.24 (±4.06)
400 mg iv	706.0 (±99.0)	181.3 (±25.9)	127.1 (±18.9)	63.5 (±7.4)
<b>Amount Excreted mg (± S.D.)</b>				
250 mg dose	54.38 (±36.22)	26.79 (±11.78)	22.84 (±6.79)	8.90 (±4.25)
500 mg dose	64.51 (±25.06)	47.37 (±15.65)	39.54 (±11.17)	15.52 (±5.39)
750 mg dose	68.90 (±41.85)	72.43 (±33.13)	61.07 (±21.68)	28.11 (±7.64)
200 mg iv	58.8 (±9.3)	13.6 (±3.2)	14.1 (±9.0)	7.5 (±2.5)
400 mg iv	125.0 (±7.2)	24.1 (±4.7)	35.1 (±12.7)	15.7 (±3.9)

Note: IV dose administered over 30 minutes.

### **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  $^{14}\text{C}$ -labelled ciprofloxacin to six healthy male volunteers (age:  $25.0 \pm 1.46$  years, weight:  $70.0 \pm 3.39$  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%.

Following the intravenous administration of a single 107 mg dose of  $^{14}\text{C}$ -labelled ciprofloxacin to six healthy male volunteers (age:  $23.7 \pm 1.89$  years, weight:  $80.2 \pm 3.45$  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:  $26.8 \pm 9.7$  yrs, weight:  $63.9 \pm 6.4$  kg), approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. After a 200 mg IV dose, urine concentrations of ciprofloxacin usually exceed 200  $\mu\text{g/mL}$  during the first two hours after dosing, and are generally greater than 10  $\mu\text{g/mL}$  at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing. Approximately 15% of an IV dose is recovered from the feces within 5 days after dosing, which may arise from either biliary clearance or transintestinal elimination. Following intravenous administration, approximately 10% of the dose is recovered in the urine in the form of metabolites.

## FACTORS INFLUENCING THE PHARMACOKINETICS

### Age (Elderly)

In 4 females and 6 males, (age:  $67 \pm 4$  years, weight:  $65 \pm 6$  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:  $24 \pm 3$  years, weight:  $72 \pm 9$  kg). The time to peak serum concentrations, overall elimination half-life and urinary recovery of ciprofloxacin were similar in both age groups.

**Table 14: Comparison of Pharmacokinetic Parameters between Healthy Elderly and Healthy Younger Volunteers**

Parameter	Elderly Volunteers (mean $\pm$ S.D.)	Younger Volunteers (mean $\pm$ S.D.)
$C_{\max}$ (mg/L)	$1.8 \pm 0.5$	$1.3 \pm 0.4$
$t_{\max}$ (hr)	$1.2 \pm 0.3$	$1.2 \pm 0.1$
$t_{1/2}$ (hr)	$3.7 \pm 0.9$	$3.3 \pm 0.6$
Total AUC (mg•h/L)	$7.25 \pm 2.45$	$5.29 \pm 1.21$
% 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:  $51 \pm 9$  years) with normal renal function (see Group I, [Table 15](#)) were compared to 6 patients (3 male, 3 female, age:  $63 \pm 6$  years) with renal impairment (see Group II, [Table 15](#)) and to 5 patients (2 male, 3 female, age:  $63 \pm 6$  years) with end-stage renal failure, treated by haemodialysis (see Group III, [Table 15](#)). 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 15](#)).

**Table 15: Mean Pharmacokinetic Parameters for Ciprofloxacin Following a Single 250 mg Oral Dose in Healthy Volunteers and in Patients with Renal Insufficiency**

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

The pharmacokinetics of ciprofloxacin following multiple IV doses were compared in subjects with normal renal function and in subjects with various degrees of renal impairment (see [Table 16](#), Groups 1-4). Patients with renal insufficiency had significantly increased concentrations of ciprofloxacin, M1 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, M1 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 16](#) 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, M1 and M2 metabolites. Group 6 in [Table 16](#) shows the pharmacokinetic results for the group dosed two hours before hemodialysis.

**Table 16: 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/1.73m <sup>2</sup>	IV Ciprofloxacin Dose	Parameter								
			Ciprofloxacin			M1 (desethylene ciprofloxacin)			M2 (sulfociprofloxacin)		
			AUC <sub>0-∞</sub> (mg•hr/L)	C1 <sub>r</sub> (L/hr)	t <sub>1/2</sub> (hr)	AUC <sub>0-∞</sub> (mg.hr/L)	C1 <sub>r</sub> (L/hr)	t <sub>1/2</sub> (hr)	AUC <sub>0-∞</sub> (mg•hr/L)	C1 <sub>r</sub> (L/hr)	t <sub>1/2</sub> (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 CIPRO<sup>®</sup> 750 mg every 12 hours for a total of nine doses followed by a 1 week washout and then a 30 minute infusion of CIPRO<sup>®</sup> I.V. 200 mg, there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

### **Food**

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

### **Drug Interactions**

#### **Theophylline**

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

#### **Caffeine**

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

#### **Multivalent Cations**

Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, Videx<sup>®</sup> (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  $C_{max}$  and AUC of ropinirole of 60 and 84%, respectively. Ciprofloxacin may increase the systemic toxicity of ropinirole.

**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 ( $V_{d_{area}}$ ) 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 ( $V_{d_{ss}}$ ) and  $V_{d_{area}}$  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 IV.

The results of this study were as follows:

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

[Table 17](#) summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

**Table 17: Distribution of Ciprofloxacin in Human Tissue/Fluid**

<b>Tissue/Fluid</b>	<b>No. of Patients</b>	<b>Single Dose of Ciprofloxacin</b>	<b>Peak Concentration (mg/kg or mg/L)</b>	<b>Mean Serum Concentration (mg/L)</b>	<b>Time After Dose (hr)</b>
Skin Blister Fluid	6	500 mg po	1.4 ± 0.36	2.3 ± 0.7	1 - 6
Bone	4	750 mg po	1.4 ± 1.0	2.9 ± 2.2	2 - 4
Gynecological Tissue	18	500 mg po	1.3 ± 0.66 to 1.6 ± 0.97	1.4 ± 0.87	2 - 4
Prostatic Tissue	1	500 mg po	3.76	1.84	2.5
Muscle	4	250 mg po	2.4 ± 1.0	2.9 ± 2.2	2 - 4
Nasal Secretions	20	500 mg po	1.4 ± 0.81	1.8 ± 0.48	1 - 3
Bronchial Tissues	10	200 mg iv	3.94 ± 2.5	1.62 ± 0.7	0.97
Vagina	18	100 mg iv	1.13 ± 0.2	0.61 ± 0.12	0.5
Ovary	18	100 mg iv	1.00 ± 0.23	0.61 ± 0.12	0.5

## TOXICOLOGY

### Acute Toxicity

<u>Species</u>	<u>Mode of administration</u>	<u>LD<sub>50</sub> (mg/kg)</u>
Mouse	p.o.	approx. 5000
Rat	p.o.	approx. 5000
Rabbit	p.o.	approx. 2500
Mouse	i.v.	approx. 290
Rat	i.v.	approx. 145
Rabbit	i.v.	approx. 125
Dog	i.v.	approx. 250

### Chronic Toxicity

#### **Subacute Tolerability Studies over 4 Weeks**

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

Parenteral administration: In the highest-dose group in each case (rats 80 mg/kg and monkeys 30 mg/kg), crystals containing ciprofloxacin were found in the urine sediment. There were also changes in individual renal tubules, with typical foreign-body reactions 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 V<sub>79</sub> 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 occurred only after high doses, with correspondingly high levels of crystalluria. For example, although they always caused crystalluria, even high doses were tolerated over 6 months without damage and without foreign-body reactions occurring in individual distal renal tubules.

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

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

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

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

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